Endocrinology

The Bulletin of the

Association for the Study of

Internal Secretions

CONTENTS

THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

ANNOUNCEMENT

THE object of this Association is to correlate the work and interests of many physicians and students throughout the world who are engaged in the study of the internal secretions and rganotherapy, and by concerted effort to broaden knowledge in this field.

This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. · The opthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about by endocrine defects and there is a large and increasing literature dwelling upon the diagnostic and therapeutic phases of this subject. In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

Reputable physicians and investigators are eligible for membership. The annual dues are $6.00, payable in advance. This includes a subscription to ENDOCRINOLOGY, the Association's bi-monthly bulletin.

The subscription price of ENDOCRINOLOGY to non-members is $6.00.

Further information and application blank may be secured by addressing the secretary, F. M. Pottenger, M.D., 1045-1047 Title Insurance Bldg., Los Angeles, California.

Endocrinology

The Bulletin of the

Association for the Study of

Internal Secretions

CONTENTS

THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

ANNOUNCEMENT

THE object of this Association is to correlate the work and interests of many physicians and students throughout the world who are engaged in the study of the internal secretions and organotherapy, and by concerted effort to broaden knowledge in this field.

This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. The opthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about endocrine defects and there is a large and increasing literature welling upon the diagnostic and therapeutic phases of this subject In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

Reputable physicians and investigators are eligible for membership. The annual dues are $6.00, payable in advance. This includes a subscription to ENDOCRINOLOGY, the Association's bi-monthly bulletin.

The subscription price of ENDOCRINOLOGY to non-members is $6.00.

Further information and application blank may be secured by addressing the secretary, F. M. Pottenger, M.D., 1045-104" ~ tle Insurance Bldg., Los Angeles, California.

Endocrinology

The Bulletin *of the*

Association *for the* Study *of*

Internal Secretions

CONTENTS

THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

ANNOUNCEMENT

THE object of this Association is to correlate the work and interests of many physicians and students throughout the world who are engaged in the study of the internal secretions and organotherapy, and by concerted effort to broaden knowledge in this field.

This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. The opthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about by endocrine defects and there is a large and increasing literature dwelling upon the diagnostic and therapeutic phases of this subject. In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

Reputable physicians and investigators are eligible for membership. The annual dues are $6.00, payable in advance. This includes a subscription to ENDOCRINOLOGY, the Association's bi-monthly bulletin.

The subscription price of ENDOCRINOLOGY to non-members is $6.00.

Further information and application blank may be secured by addressing the secretary, F. M. Pottenger, M.D., 1045-104ʳ ˅ tle Insurance Bldg., Los Angeles, California.

Endocrinology
The Bulletin *of the*
Association *for the* Study *of*

Internal Secretions

CONTENTS

THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS

ANNOUNCEMENT

THE object of this Association is to correlate the work and interests of many physicians and students throughout the world who are engaged in the study of the internal secretions and therapy, and by concerted effort to broaden knowledge in this

This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. The opthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about by endocrine defects and there is a large and increasing literature dwelling upon the diagnostic and therapeutic phases of this subject. In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

Reputable physicians and investigators are eligible for membership. The annual dues are $6.00, payable in advance. This includes a subscription to ENDOCRINOLOGY, the Association's bi-monthly bulletin

The subscription price of ENDOCRINOLOGY to non-members is $6.00.

Further information and application blank may be secured by addressing the secretary, F. M. Pottenger, M.D., 1045-1047 Title Insurance Bldg., Los Angeles, California.

Endocrinology
The Bulletin *of the*
Association *for the* Study *of*
Internal Secretions

CONTENTS

ANNOUNCEMENT

THE object of this Association is to correlate the work and interests of many physicians and students throughout the world who are engaged in the study of the internal secretions and otherapy, and by concerted effort to broaden knowledge in this ld.

This Association is not limited to specialists. It includes in its membership physiologists, pathologists and other investigators in addition to a large number of physicians in active practice—leading men in this field in the United States and thirty other countries.

Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. The opthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about by endocrine defects and there is a large and increasing literature dwelling upon the diagnostic and therapeutic phases of this subject. In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

Reputable physicians and investigators are eligible for membership. The annual dues are $6.00, payable in advance. This includes a subscription to ENDOCRINOLOGY, the Association's bi-monthly bulletin.

The subscription price of ENDOCRINOLOGY to non-members is $6.00.

Further information and application blank may be secured by addressing the secretary, F. M. Pottenger, M.D., 1045-104⁷ ⊤'tle Insurance Bldg., Los Angeles, California.

ORGANOTHERAPY, PRESENT ACHIEVEMENTS AND FUTURE PROSPECTS*

H. LISSER, A.B., M.D.

Asst. Clin. Prof. of Medicine and Chief of the Ductless Gland Clinic,
University of California Medical School

SAN FRANCISCO

INTRODUCTORY

Since the membership of this Academy is representative of all branches and specialties of clinical medicine, it has seemed judicious to select for this address a phase of endocrinology interesting to all practitioners. Although this youthful field of internal medicine may be regarded by some as rather narrow, arrogant and obstreperous, it does in truth reach out and touch closely each and all of the subdivisions of medical practice and preclinical investigation. A brief elaboration of this conception may not be inappropriate at this point.

Thus, the opthalmologist has occasion to notice exopthalmos and the other "eye signs" of thyroid disease; or be the first to suspect diabetes mellitus because of retinal abnormalities; he will be called upon to determine precisely the degree of bitemporal hemianopsia or diminution of vision in instances of pituitary tumor that impinge upon the optic chiasm. Indeed he has gone further and attempted to abort an early cataract with thyroid extract (with some success), and is giving serious con-

---

* Address delivered before the Portland Academy of Medicine, Portland, Oregon, Nov. 13, 1924. Lantern slides were used to illustrate the paper, which are not reproduced in this publication.

sideration to the incretory origin of glaucoma. The otorhino-laryngologist may recognize a myxedematous infiltration of the Eustachian tubes as the cause of a patient's deafness; he may notice the nasal deformity of acromegaly, the saddle nose of cretinism, the thick tongue of hypothyroidism. Some of his confreres have contributed some thoughtful speculations as to an endocrine responsibility for certain forms of asthma and vasomotor rhinitis. And it may be noted in this connection that the occasional sudden and considerable gain in weight following tonsillectomy in some children is not without endocrine significance.

The orthopedist will be consulted for myalgic and arthritic aches and pains, which may depend upon the excessive strain of an endocrine adiposity; or he may perceive that a progressive kyphosis and bulging sternum is merely a feature of an acromegalic hypophysis. The urologist will be consulted by anxious parents because their son's genitalia retain an infantile appearance; and they will be besieged by anxious husbands who fear lest they "lose their manhood" or who yearn for rejuvenation. The gynecologist does not lack for patients suffering from "hormonic imbalance"; indeed, it is essential that he be alert and alive to the fact that a "fallen womb" is not the invariable explanation of dysmenorrhoea; and that hypothyroidism may cause menorrhagia and hypopituitarism cause amenorrhoea, and that neither can be diagnosed through a speculum. He should be aware of the fact that some cases of sterility respond to glandular therapy, and that menopausal symptoms are often alleviated by ovarian extracts. The obstetrician may well be grateful for pituitrin, and the surgeon for adrenalin.

Surgical achievements have contributed most fruitfully to both the clincial and experimental study of endocrinopathies, and ingenious operative procedures are constantly utilized to afford relief to patients with ductless gland disease. One need but mention thyroidectomies, sella decompressions, removal of ovaries, testicles, and hypernephromata. The pediatrician is frequently confronted with preadolescent disturbances of glandular function, and should be intimately familiar with the signs and symptoms of gigantism, childhood myxedema, status thymicolymphaticus, the several types of infantilism, and the pineal, adrenal and gonadal types of sexual precocity.

The dermatologist observes trophic disturbances of skin, hair and nails that are attributable to hypothyroidism, hypopituitarism, hypogonadism, or under-function of the chromaffin system. The neurologist and psychiatrist encounter instances of mental retardation, epilepsy, tetany, constitutional inferiority, psychosis and even mania that may have an endocrine explanation and subside under glandular therapy.

The cardiologist finds much to interest him in the tachycardia and arrthymias of thyrotoxicosis; the gastroenterologist realizes that an acute thyroid crisis may cause severe vomiting and diarrhoea; the metabolic expert is concerned with the chemistry of diabetes mellitus, diabetes insipidus and endocrine obesity.

Nor do the ramifications of endocrinology end even here. The administrator of public health is applying the results of endocrine research to the prophylactic eradication of goiter. The student of eugenics finds much to stimulate him in a consideration of inherited endocrine characteristics. It would require a lengthy recital to adequately acknowledge the debt we owe anatomists, physiologists, pathologists, pharmacologists and chemists, many of whom have vitally enriched our knowledge of the hormonopoietic system, and to whose continued researches we rightfully and confidently look for crucial aid in the solution of many endocrine problems.

There is no denying a broad horizon to this important field of medicine. Indeed, its fascinations have leaped the boundaries of our profession and today intrigue the laity. Unfortunately, as might be expected, the popular magazine and Sunday supplement have chosen, for the most part, those spectacular and least reliable features of the subject which could be calculated to appeal to the modern craving for the sensational. Hence it happens that the average layman's conception of the ductless glands centers embarrassingly around the organs of sex and their weird counterparts—"monkey glands," so much so that his newspaper acquaintance with "goats' glands" and "Black Oxen" forbid their association in his mind with such refined diseases as goiter and diabetes.

It behooves us, therefore, to be reasonably well informed as to the present possibilities, and perhaps even more as to the present limitations of organotherapy, and it is the endeavor of

this paper to summarize its present status, and to mention some of the hopes that we may legitimately entertain for its future.

DEFINITION OF ORGANOTHERAPY

The term, organotherapy, as used in this paper, refers to the therapeutic use of ductless gland substance for the alleviation of an endocrine disease. This restrictive definition at once excludes extracts derived from organs that are not at present considered members of the hormonopoietic system; such as bone marrow extract, brain substance, extracts of gastric or duodenal mucosa, kidney substance, liver substance, spleen substance and extract of tonsil or lymph gland. Indeed, Schafer, in the latest edition of his excellent work, "The Endocrine Organs," omits the thymus from the group of glands "to which we now commonly ascribe internally secreting functions," since no appreciable result is obtained from the removal of this organ, and since no reliable evidence has been presented that its extract has an "endocrine function" in the strict sense of that term.

Furthermore, organotherapy, as dealt with in this paper, does not include the use of ductless gland extracts for conditions or diseases whose incretory origin is uncertain or unlikely. *It is important, whenever possible, to make a clean-cut distinction between true specific supplementary substitution therapy for the relief of an incretory deficiency, and the administration of a ductless gland extract for its druglike pharmaco-dynamic effect.* Thus, the exhibition of thyroid extract in myxedema is an example of the former, whereas the injection of pituitrin to hasten labor is an example of the latter. It would be quixotic to diagnose hypopituitarism, merely because a phlegmatic uterus is stimulated to contract by pituitary extract. An injection of adrenalin may be a life-saving procedure in anaphylactic shock; it affords almost immediate though temporary relief from the intolerable urticaria of serum sickness; it shrinks mucous membrane when locally applied and is very useful, in operations under local anaesthesia, to diminish bleeding; its injection is a blessing to a patient in the throes of an asthmatic attack; but all these highly successful and desirable effects are pharmaco-dynamic, and do not signify the relief of an underlying adrenal deficiency. There must be no confusion on this point, if we are to evaluate properly the role of organotherapy in the treatment

of ductless gland disease. It is only fair to add that this distinction is not always possible. For example, we are not yet certain as to whether the remarkable, though transitory, reduction of thirst and polyuria in diabetes insipidus by injections of pituitrin is indicative of a pituitary origin for this disease, or whether the effect is a pharmaco-dynamic check upon a supposed metabolic center in a diseased hypothalamus.

It is axiomatic that a gland extract should never be administered when the corresponding gland of the patient is in a state of hyperfunction. No good can come from adding fuel to the flames. It would hardly seem necessary to mention so obvious a doctrine, were it not for the fact that some physicians still prescribe thyroid extract for goiter and pituitary extract for acromegaly, even though the goiter in question be toxic, and the acromegaly be evidence of hyperpituitarism. An unanalyzed syndrome is a quicksand for therapy.

Extracts of one gland are sometimes used to combat or antagonize excessive activity of another gland. Thus, Marine has reported favorable results from the administration of adrenal substance in cases of exopthalmic goiter; pituitary extract has been utilized for the same purpose (Solis-Cohen, Hector Mackenzie, Sir James Barr, etc.). Kate Knowles, in Kashmir, has treated osteomalacia with pituitary extract, upon the assumption that it would counteract an ovarian hyperplasia, which latter condition was supposed to be responsible for the excessive excretion of calcium. None of these procedures has received sufficient confirmation to warrant widespread use. They remain, for the present, interesting clinical experiments.

Our chief concern, then, is with that type of organotherapy which attempts to supplement a specific endocrine deficiency by supplying, from exogenous human or animal gland substances, that amount of hormone which the patient's diseased gland is unable to secrete; with the ideal purpose of having the endogenous patient's hormone plus the exogenous artificially administered hormone equal a normal amount of normal hormone.

CLASSIFICATION OF GLANDULAR PRODUCTS

How near have we come to reaching this goal with the commercial products at present available? A fairly extensive expe-

rience with modern glandular preparations leads me to classify their practical usefulness as follows.

CLASS A—*Includes those endocrine extracts which are standardized, strongly potent, uniformly reliable and specific; and which, when properly administered under appropriate circumstances, will yield consistent and convincing results.*

There are certainly two and possibly three such extracts; first, *thyroid extract or thyroxin*, as used in the treatment of childhood and adult myxedema and the milder grades of hypothyroidism; *second, insulin*, as used in diabetes mellitus to supplement a deficiency of pancreatic island hormone. *The doubt about the third extract, pituitrin*, an extract of the posterior lobe of the hypophysis, hinges upon the pituitary origin of diabetes insipidus. Its action in this disease is as specific as that of insulin in diabetes mellitus, and if diabetes insipidus is finally proven to be due to a hypofunction of the pars intermedia or posterior lobe of the hypophysis, then pituitrin will deserve to be grouped in Class A. The hormone, adrenalin, though standardized, potent and even synthetized, is not entitled to a place in Class A, since it has not, to my knowledge, been consistently or convincingly effective in the relief of the only adrenal deficiency syndrome that we are sure of, namely, Addison's disease. Its brilliant pharmaco-dynamic effects are not to be accounted for on the assumption that this synthetic hormone has compensated for a lack of endogenous epinephrin.

It is hardly necessary to comment on the value of insulin. Since its discovery and introduction, about two years ago, an amazingly rich literature has accumulated. It need only be emphasized that its very strength and specificity forbids any negligence in the accurate control of the diet of a diabetic. On the contrary, a rigid quantitative supervision is imperative, for overdosage with insulin is fraught with danger, unless promptly relieved by the administration of glucose.

The usefulness of thyroid extract in the treatment of childhood and adult myxedema, and its control by repeated estimations of the basal metabolic rate, is well established and remains one of the most brilliant contributions to medical therapeutics. No further comment on this score is necessary except again to call attention to the lamentable fact that most of these patients pass through the hands of many physicians before the correct

diagnosis is made. In 1920, Anders found that in 55 cases of myxedema collected from the American and Canadian literature, 74 per cent had failed of diagnosis by one or more physicians: this observation was reiterated by Hoskins in 1922. In 1924, at a meeting of The Association for the Study of Internal Secretions, Boothby stated that not one of the many cases of myxedema studied at the Mayo Clinic arrived in Rochester with a diagnosis of myxedema. At the University of California medical school we have had an exactly similar experience. In the majority of adult cases it is one of the easiest of diagnoses to make, and its repeated confusion (because of puffy eyelids) with Bright's disease is truly deplorable.

The milder forms of hypothyroidism are not so readily recognized, although the difficulties have been diminished by determinations of the basal metabolism. A moderately low (10 per cent to 25 per cent minus) rate will be found not infrequently. In instances where the clinical picture is suggestive, but the basal rate falls within normal limits, a therapeutic trial of thyroid extract, under careful observation, is justifiable and will occasionally yield gratifying results. The dictum that thyroid extract is contraindicated unless the patient's metabolic rate is below normal is no longer tenable.

The scope of this paper forbids consideration of the many "little signs" of hypothyroidism. It may not be out of place, however, to bring to your attention an interesting syndrome which I would term: *Adolescent Menorrhagia of Hypothyroid Origin.* A conversation with Slemons in 1922 first suggested the possible benefit to be derived from thyroid extract in certain cases of irregular and very profuse bleeding in young girls. A further study and analysis of this condition has convinced me of the existence of such a syndrome. In the absence of local causes within the pelvis, an early onset of menstruation (9 to 12 years of age) together with long continued and copious bleeding is very suggestive of hypothyroidism. Early maturity with early development of secondary sex characters are the dominant characteristics of this syndrome. There may be little else in the clinical picture to indicate deficiency of thyroid secretion. I am, of course, not referring to those remarkable examples of precocious puberty due to suprarenal cortex tumors, where development of breasts, appearance of pubic hair and onset of menstru-

ation may occur at the very early age of two to six years or thereabouts.

As a typical example of this menorrhagia of puberty I would cite the following case in a girl of 16 years, who began to menstruate at the age of 11½. Periods would occur at irregular intervals, but would last from six weeks to three months, and the flow on some days would be so copious as to require fourteen pads in twenty-four hours. There was nothing whatever in this girl's appearance to suggest hypothyroidism: skeletal growth, bodily proportions, weight, skin and facial appearance being quite normal. When I first saw her, in April, 1923, she had been flowing continuously, slightly or copiously, since Nov. 14, 1922, a period of five months. Her basal metabolic rate was 23 per cent minus. She was placed on thyroid extract (Armour) grains one daily, which was gradually increased to grains four daily. In June, 1923, her rate was 4 per cent plus, and in September, 1923, 9 per cent minus. She ceased flowing April 26th, ten days after beginning treatment. Subsequent periods occurred as follows: May 25-June 20, July 8-22, Aug. 9-22, Sept. 4-9, Sept. 26-30, Oct. 19-23, Nov. 10-14, Dec. 7-11, Jan. 4-8, and since then regularly every twenty-eight days for four or five days, the amount of the flow having become normal.

I venture to consider such evidence incontestable.

CLASS B—*Includes those endocrine substances which, in the hands of trustworthy clinicians, have produced remarkable improvement in specific deficiency syndromes, where the favorable response to the gland administered seems incontrovertible; but where such satisfactory results have not occurred with sufficient dependability or consistency to justify placing the extracts in Class A.*

There are three gland substances or extracts, in my opinion, which under particular forms of administration and in certain types of endocrine disease, warrant their inclusion in this Class B.

PITUITARY EXTRACT

Skeletal undergrowth is an outstanding feature of lack of anterior lobe hormone. Some authors, notably McGraw of Detroit in a recent careful study, have reported increased growth from oral administration of anterior lobe pituitary substance. Perseverance over at least a year's time is absolutely essential. Therapy over a few weeks or months is wasted time and money. My own experience has been encouraging in several instances, where it was stated that no growth had occurred for several years prior to instituting treatment, but the results have not been sufficiently spectacular to convince me that they could without question be ascribed to the gland therapy administered. Furthermore, Professor Evans of the University of California

has very kindly tested several of the commercial pituitary preparations on rats, both by feeding and injection, comparing the rate of growth of the treated animals with untreated litter mate controls under identical conditions. The results were entirely negative. These complete failures are to be contrasted with the remarkable gigantism he has produced in rats with an anterior lobe substance which he has prepared in his laboratories, but which is not yet available for trial on human beings. These important experiments will be referred to again later. *The commercial anterior lobe substances, therefore, in so far as stimulation of growth is concerned, probably do not deserve classification in Class B, and certainly not in Class A.*

A second important characteristic of hypopituitarism origination prior to adolescence is retarded sexual development, including: absence of secondary sex characters at an age when they should have appeared: and in girls late onset of menstruation with prolonged intervals and scanty flow; and in boys an infantile appearance of the external genitalia with absence of the prostate gland. To what extent does therapy with anterior lobe pituitary substance influence this syndrome? Occasional benefit has been reported and I have personally observed many instances which encouraged the belief that the gland administered had been responsible for the improvement noted. But here again we are confronted with the difficulty of being certain that the changes might not have occurred without treatment, especially in boys and girls treated between the ages of 11 and 15 years, a period when nature is apt to take command quite suddenly; and yet these are just the years when therapy should be undertaken if the boy or girl presents unmistakable signs of genital infantilism.

There can be no question, however, of the splendid results obtainable from anterior lobe and whole pituitary substance in post-adolescent hypopituitarism (without tumor). Especially gratifying and convincing is the effect produced in that not uncommon type of hypopituitarism in women between the ages of 18 and 35, which is characterized by rather sudden accumulation of a girdle adiposity, with gradually increasing intervals between menstrual periods and a flow so scanty as to require but one or two pads for the entire period; this not infrequently culminates in complete amenorrhoea.

A woman at the age of 32 years had a severe influenzal infection. She rapidly gained 75 lbs. and ceased menstruating. She came under my observation at the age of 37, having had complete amenorrhoea for five years. Her basal metabolism was normal. She received anterior lobe substance by mouth, fifteen grains daily, and menstruated one month later. Thinking she was cured, she remained away for three monthts and discontinued the medicine. She skipped three periods. Then she returned for further treatment. For the next six months she took anterior lobe (Armour) regularly, gradually reducing the dose from fifteen to six grains daily, and menstruated regularly and copiously.

Another woman gave a similar history, amenorrhoea beginning at the age of 26 years. Treatment was instituted when she was 32 years old, and the first period in six and one-half years occurred six months later; the next period occurred six months later, then one followed three months later, then two months later, and then five weeks later. She also lost 50 lbs. under treatment.

The writer has had many successful experiences in regulating the menstrual cycle to a twenty-eight or thirty day interval in girls and women, whose previous periodicity had varied from five weeks to three months. It would seem unduly critical to doubt the specificity of such glandular therapy, and therefore *anterior lobe substance is entitled to a place in Class B, in so far as its effect on post-adolescent aneoplastic hypopituitarism is concerned.*

A third important characteristic of hypopituitarism, both prior and subsequent to adolescence, is obesity. For the most part this adiposity is strikingly confined to the lower chest, intrascapular regions, abdomen and hips, and is conspicuously absent from the neck, upper chest, upper back, arms and legs. in cases unassociated with hypothyroidism. This type of adiposity is referred to as girdle obesity. If one not only records the weight but also the circumferential measurements at various levels, one will find at times a redistribution of this obesity (Beck) with but little loss of weight; and in most instances a loss of several inches around the waist, abdomen and hips, under pituitary therapy. It is true that in many cases better results are achieved if thyroid extract is combined with the pituitary substance. It must not be inferred, however, that the reduction so obtained is entirely due to the thyroid extract, and that the pituitary factor is negligible or imaginary. Beck, Timme, Englebach and Tierney and the writer have all obtained reductions that seem incontestable. *In a recent paper on endogenous endocrine obesity I have referred to several cases in which a loss of 20 to 50 lbs. was secured by pituitary extract alone.* I am

inclined to believe that success is more likely if the pituitary substance is prescribed in tablets or capsules that are coated with salol, on the assumption that more unaltered absorption takes place from the intestines with less likelihood of harm from gastric acidity.

In this connection I might mention a recent conversation with Professor Evans in which he divulged the disappointing news that neither pituitrin (extract of the posterior lobe) nor his anterior lobe extract reduces the adiposity of partially hypophysectomized rats. This suggests one of two conclusions, either that the adiposity is partly of cerebral' and not purely pituitary origin (as claimed by Camus and Roussy and Bailey and Bremer), or that the otherwise potent pituitary extracts of Evans do not contain the fat-reducing hormone. *It is the uncertainty of this situation experimentally, and the inconsistency of clinical results, which prompts the writer to place whole pituitary substance, as a fat-reducing extract, in Class B, rather than Class A.*

The commercial preparations of desiccated testicular substance for oral use, and the liquid extracts for injection purposes are probably almost inert. To quote one of the foremost endocrinologists, Falta, "The drug therapy of sexual glandular insufficiency has as yet had in man no decisive results. The feeding with testicular substance is but little carried out, and the reports as to the result of injection of sexual glandular extracts disagree. Spermin (Poehl) may have a certain stimulating action on the nervous system, but profound symptoms of insufficiency are hardly improved thereby." The testicular products, therefore, obtainable from manufacturing firms, are not entitled to a place in Class B, let alone Class A

The world-wide interest in sex gland transplantations and implantations, however, cannot be brushed aside merely because of the sensational appeal involved. Unquestionable and remarkable improvement has been obtained in many instances of early and late eunuchoidism, and the evidence presented will withstand scrutiny. Not only have there been extraordinary transformations in the subjective sphere, such as increased energy, feeling of well-being, greater capacity for work and return of

libido, but what is far more important and reliable in judging the efficacy of a therapeutic agent, striking objective changes as well, such as increased size of genitalia, growth of hair, changes in weight and alterations in skin and nails.

Dr. Nixon, associated with me in the Ductless Gland Clinic, published the following case. A boy of 18 years, six feet one inch tall and weighing 197 lbs., came under our observation because of lethargy, weakness, inability to work or concentrate, and momentary attacks of unconsciousness (petit mal). He was tall, fat distribution was markedly feminine, including broad pelvis, mammary fat and mons veneris padding; he had shaved only three or four times; pubic hair was of feminine type, and voice was still high pitched. Basal metabolism was normal. He received three implantations, three months apart, of fresh semi-solid untreated ram's testicular substance, forcibly injected into the abdominal wall. This testicular material was obtained through the courtesy of Dr. Stanley, and the method of implantation followed exactly the procedure first suggested by him. The change from a whining, lackadaisical, effeminate boy to a vigorous, upstanding young man earning his living was so marvelous that I would have suspected some psychic magic if it were not for unmistakable evidence, such as loss of 25 lbs., growth of beard and change of voice.

I have recently recorded a case of onychauxis in a eunuchoid (whose gonad insufficiency dated from direct trauma with subsequent sloughing of the testicles), in whom the rough-ridged shell-like appearance of finger and toe nails changed to smooth, normal nails after testicular implantations. Photographs of the nails before and after treatment were published as proofs.

More extensive clinical studies may be found in the writings of Steinach, Lichtenstern, Lespinasse, Lydston, Thorek, Stanley, Vecki, and others, which prove beyond question that *strikingly beneficial results are often obtained by transplantation or implantation of human or animal (usually monkey or ram) testicular substance into boys and men who are victims of hypogonadism. This judgment is not to be construed as applying to the same procedure when used in Ponce de Leon strivings for rejuvenation or longevity, the premature exploitation of which does not redound to the credit of some members of our profession.* Testicle implantations for testicle deficiency have yielded positive results sufficient to justify classifying this substance, when thus administered, in Class B.

OVARIAN PRODUCTS

It is rather odd that we still know so little concerning the clinical attributes of ovarian dysfunction. Since menstruation must be intimately associated with ovarian function, we have, rather crudely, concluded that hyperfunction must result in excessive uterine bleeding or menorrhagia, and that hypofunc-

tion culminates in amenorrhoea. As a matter of fact, excessive menstruation (when not due to infection, polyp or tumor within the pelvis) is probably due to hypothyroidism and only secondarily to ovarian disturbance; and amenorrhoea is more often primarily dependent on hypopituitarism and only secondarily on a deficient ovarian secretion. It is, furthermore, surprising that despite the wholesale ovarian castrations of the past fifty years, our knowledge of the clinical consequences is relatively meager, being confined largely to three phenomena: vasomotor symptoms, amenorrhoea and obesity. Extreme hypofunction of the ovaries prior to puberty is supposed to permit the anterior lobe of the pituitary to run rampant as it were, resulting in tall eunuchoid giants, with marked disproportion between the long extremities and relatively short trunk. It is also supposed to produce a certain type of localized adiposity confined to trochanteric fat pads. Menstruation either does not occur at all, or is late in onset.

To what extent can these disturbances be rectified by ovarian extracts? There is no lack of ovarian preparations on the market, both for oral use and injection, consisting of the whole ovarian substance, corpus luteum extract, and an extract of the material that remains after removal of the lutein tissue, called ovarian residue. *It would appear, accordingly, that there must be definite indication for the use of either lutein, ovarian tissue without lutein, or the entire gland, whereas the notions of most of us in regard to such distinctions are exceedingly vague and confused.* The writer's experience coincides with that of Novak, whose appraisal of ovarian therapy in 1922 applies equally well to the situation at the end of 1924. The gist of his conclusions can be summarized in the statement that *the indications for ovarian therapy are still ill defined, and that the commercial products available have achieved but little in a quarter century of trial, beyond a very definite relief of the vasomotor symptoms of the menopause.* And it may be noted with reference to the last item, that the earlier the artificial menopause, the more aggravated the symptoms and the less efficacious the ovarian tablets, capsules or ampoules. There will be many to disagree with this lugubrious view of ovarian therapy, but it may be accepted as a general rule that there is far less enthusiasm shown in reporting failure than in recording success. At the same time I freely

confess that I have used and still use ovarian preparations, and have occasionally achieved surprising results, especially in the relief of different sorts of subjective symptoms. but the magic powers of "the glands" have seemed more convincing to the patient than to me. *In so far as the alleviation of menopausal symptoms is concerned, ovarian extracts deserve classification in Class B.*

OVARIAN TRANSPLANTATIONS AND IMPLANTATIONS

It is curious that far less interest has been manifested in ovarian implantations than the corresponding procedure in the male sex, despite the fact that ovarian castrations are infinitely more common than testicular castrations. I have not had any personal experience with this procedure, but plan to use it shortly. Falta cites the two following cases:

"Cranner transplanted into a twenty-one-year-old girl, who had never menstruated and who possessed rudimentary mammae, the ovary of an osteomalacic woman. Menstruation then set in and the breasts developed. Still more remarkable is the case of Halliday-Crom. In this case amenorrhoea had set in after labor and symptoms of absence developed. The small cystic ovaries were removed and a foreign ovary implanted. The woman again menstruated four months after the operation, and four years after the operation she conceived and bore a normal child. This case was earnestly discussed before the Edinburgh Obstetrical Society, and can not well be denied. There is, indeed, in this case no doubt that if there has been no error of observation, this woman bore the child of another woman. Serious objections might be raised against such procedures on ethical and forensic grounds.

"Sippel reports from Bumm's service four cases in which previously sterile women conceived and passed through a normal pregnancy after the sluggish function of the otherwise normal ovary had been roused and speeded up by transplantation in the abdominal wall (prevesical space) of two disks of ovarian tissue still warm from the body of another woman. These grafts were taken from women being hysterectomized for cancer, myoma or pulmonary tuberculosis."

These results are so striking that further trial of this method of ovarian therapy seems advisable, although great caution should be exercised in the selection of the ovarian tissue to be grafted. It at least constitutes an immense advance over the indifferent results ordinarily obtained from the present commercial products.

We have now given consideration to the practical usefulness of insulin, thyroid, pituitary, ovarian and testicular extracts.

CLASS C—*includes all other endocrine extracts at present available, where it is conceded that occasional benefit may have been obtained from their employment in a variety of conditions;*

but only infrequently and as yet insufficiently to justify their use in general practice. In this group belong parathyroid, pineal, adrenal, thymus, prostate, mammary and placental extracts. We are not even certain that the pineal, thymus, prostate, mammary and placental organs are really incretory glands.

The above classification is based largely on my own personal experience, second on a reasonable acquaintance with endocrine literature, and third, on questions and answers in conversation with some of the leading endocrinologists of this country. The above statements hold as my views for Nov. 13th, 1924. They may be altered in the near future. We are on the threshold of great discoveries. Pancreatic extracts belonged in the Class C of inert extracts until Banting's brilliant discovery of insulin promptly advanced them to Class A. Evans may do the same before long for the anterior lobe of the hypophysis, and Allen and Doisy may shortly perform an equal service for ovarian extracts.

FUTURE PROSPECTS AND METHODS OF PROGRESS

Researches in pure science abound in fruitful possibilities whose practical translation later into endocrine investigation or therapeutics may astonish the original worker. Such occurrences cannot be systematically planned nor foreseen, but the alert investigator is constantly on the lookout for new methods in related sciences which may be applied to his own field of endeavor. It may seem a long way from the chemist in his laboratory to the clinician in his office. Unfortunately they are often farther apart than they should be. To what extent can the general practitioner and the specialist in their daily work "by the bedside" contribute to our knowledge of organotherapy? Their opportunities are great. Many of the most stimulating and important discoveries in endocrinology emanated from the clinic. One need but recall a few names out of a great number, such as Addison, Graves, Basedow, Moebius, Murray, Gull, Kocher, Marie, Halsted, Plummer, Cushing.

Precise observations, carefully controlled, may constitute data from which valuable conclusions may be deduced. The subjective rôle, both on the part of physician and patient, in judging the efficacy of any treatment, is a formidable one. This makes it all the more necessary, if one's reasonings are to possess

any 'merit, that one employ *"the one thing at a time" type of treatment.* This should be a fundamental principle in glandular therapy, at least among those clinicians who desire to record their experiences for the benefit of their colleagues. No sensible deductions can be made concerning any one drug, if several are administered simultaneously. It may be argued that the great majority of physicians are not publishing papers, and are only interested in "results."

PLURIGLANDULAR THERAPY

Let us briefly examine this *pluriglandular three-ring circus.* It is granted at once that functional upheaval in any one gland of the hormonopoietic system does not ordinarily permit of normal function in the remainder, but frequently involves one or more of them in its tribulations. But, as Sharpey-Schafer phrases it. "our knowledge regarding this is still in many respects confused." *In the enthusiasm for roping these glands together, a veritable jungle of knots has been tied that is difficult to untangle.* The doctrine of pluriglandular disease has naturally led to the doctrine of pluriglandular therapy, with the introduction of "shotgun hit-or-miss mixtures." There is a marked tendency these days to hide behind the skirts of this so-called interrelationship. *As a matter of fact, the majority of endocrinopathies which we are justified in diagnosing exhibit a predominantly uniglandular basis, which anyone properly trained in endocrine diagnosis should be able to recognize.* A firm foundation for incretory therapy demands a sharply defined analysis of the symptoms and signs, with emphasis on the gland primarily responsible.

Even if it be conceded (which of course it is) that serious disease of one gland will produce disturbed function in one or more other glands, then logic should force the conclusion that a restitution of that first gland to normal function will, ipso facto, restore the remainder to normal function. Indeed, there is experimental proof for this contention. As a result of hypophysectomies in rats and tadpoles, Evans and Smith have demonstrated alterations in thyroid and adrenals; these latter abnormalities have been corrected by replacement therapy with anterior lobe substance, without any recourse to thyroid or adrenal extract.

At any rate, if one prescribes one gland extract and watches its effects over two or three months or until no further effects are obtained, and then keeping its dose the same, adds another gland extract, clinical changes that subsequently occur may then with some logic be ascribed to the second gland administered. In this manner one may individualize one's therapy. Objection is sometimes made that this involves a waste of time when a pluriglandular mixture might have been used at the outset; as if time were any object in a type of therapy that must be continued for years. Myxedematous patients must take thyroid for life; insulin would have to be given indefinitely, if the "load" were not reduced by regulation of the sugar formers in the diet; pituitrin must be administered continuously, as a rule, in diabetes insipidus.

In any event, one can compound one's own mixtures for the individual case if one understands endocrinologic diagnosis and is acquainted with proper dosage; and if one is not familiar with both these fundamentals one should not use stock formulas. One might as well expect a dermatologist to remove a brain tumor, the only difference being that little harm comes from the use of these commercial combinations, since most of the constituents are impotent. *Fortunately, the stampede into the "endocrine gold fields" (as merrily phrased by Abel) is beginning to wane, probably because much of the ore is low grade. One of the best methods of judging the potency of an endocrine extract is to study the effects of overdosage.* An excess of thyroid extract produces unmistakable signs and symptoms of thyrotoxicosis, which should be familiar to everyone. One dare not be careless in overdosing with insulin. Excessive amounts of adrenalin and pituitrin produce annoying symptoms. We may well ask what similar alarming or dangerous symptoms are produced by very large doses of whole pituitary, anterior lobe pituitary, ovarian, testicular, parathyroid, pineal, adrenal cortex or thymus extract; probably none beyond headache or nausea!

IMMEDIATE PROSPECTS

The brilliant discoveries of the future in endocrine therapeutics will probably have their origin in elaborately planned, well endowed experimental investigations in which physiologists, chemists, pathologists, pharmacologists, biologists and clinicians—

co-operate intensively. It was that sort of group attack by Kendall, Mayo, Plummer, Wilson and Boothby that produced thyroxin; it was a similar effort by Banting, Best, Macleod, Collip and co-workers that achieved insulin. What is the present outlook for further results of like importance and unimpeachable character?

Professor Abel of Johns Hopkins, in his admirable Harvey Lecture, recently published, reviews the work of himself and associates in the isolation of the active chemical principle of the posterior lobe of the pituitary. This principle has been isolated in the form of a tartrate for which no claim is yet made as to chemical purity or individuality, but which "possesses extraordinary potency as a smooth muscle stimulant, being 1000 to 1250 times more powerful than the acid phosphate of histamine, a base which has hitherto held the ranking position in this respect." He submits proof that this tartrate "displays all of the characteristic physiological properties of a good aqueous extract of the posterior lobe of the hypophysis. In addition to its action on the uterus, it causes a prolonged rise in the arterial pressure, with constriction of the peripheral arterioles and capillaries, a brief diuresis in the green-fed rabbit, has an antidiuretic action in diabetes insipidus, and affects the respiration of dogs and rabbits in a characteristic manner." Moreover, *these brilliant researches of Abel bring strong evidence to the support of the hypothesis that the posterior lobe has an endocrine function and that it elaborates a specific hormone which controls the removal of water from the body via the kidneys and perhaps other organs, and that a deficiency of this hormone leads to a polyuria or diabetes insipidus.*

The remarkable work of Evans, Smith and associates of the University of California, also partly summarized in a Harvey Lecture shortly to be published, holds great promise for a powerful extract from the anterior lobe of the hypophysis. This extract, prepared fresh from bovine hypophyses, is now protein-free and sterile. Its concentration for clinical purposes remains to be accomplished. Its use at present would be too costly, since very large quantities would be necessary to reproduce the results in human beings experimentally attained in tadpoles and rats. The intraperitoneal injection of this anterior lobe extract brings to normality the four deficiencies that result from hypophysec-

tomy in the tadpole, in that it accelerates the growth rate; induces a normal depth of pigmentation; repairs the atrophic thyroid and interrenal bodies, the specimens metamorphosing; and reduces the fat organ to normal dimensions. The normal and thyroidless tadpoles, when injected with this anterior lobe extract, show an acceleration in their growth rate, attaining an unusually large size, and display an increased depth of pigmentation. The dwarfism of hypophysectomized rats is corrected by injections of this extract; and the secondary alterations in other endocrine organs are alleviated. No effect, however, has been obtained as yet on the adiposity that results from hypophysectomy in rats. Injections of this anterior lobe extract into normal rats produces gigantism consistently, a truly brilliant achievement.

Allen and Doisy of St. Louis have succeeded in preparing an ovarian hormone from the liquor folliculi of hog ovaries. This follicular fluid has been rendered protein free. Injections of this extract into spayed animals (rats and mice) produced typical estrual hyperemia, growth and hypersecretion in the genital tract, and growth in the mammary glands. They concluded that this hormone seems to be an efficient substitute for the endocrine function of the ovaries of the non-pregnant animal. Furthermore, these spayed animals, when in a condition of artificially produced estrus, would exhibit typical mating instincts, successful copulation occurring, which justified the conclusion that this follicular hormone is the cause of estrual or mating instincts, since these animals will only copulate in estrus. Injections of this extract into animals immediately after weaning hastened sexual maturity. These crucial results could not be duplicated by commercial extracts of ovaries, corpora lutea, and ovarian residue, from three of the largest firms manufacturing biologic products. Allen, in a paper before the Association for the Study of Internal Secretions, in June, 1924, announced that this follicular hormone was being tried clinically on a few women whose ovaries had been removed but in whom the uterus had been left intact. Clinical use on a large scale was still impractical because of the very large quantities necessary. The problems of concentration were yet to be overcome.[*]

---

[*] Since this paper was written, Collip has announced the preparation of a parathyroid extract which seems to control the calcium content of the blood.

In these three great discoveries of Abel, Evans and Smith, and Allen and Doisy, lie our immediate hopes for a more successful organotherapy with pituitary and ovarian extracts. Undoubtedly undertakings of similar magnitude will soon be under way for other important glands of internal secretion, whose extracts at present leave so much to be desired. Great difficulties and obstacles will be encountered, baffling complexities will demand solution, discouraging delays are to be expected. It took thirty years of persistent endeavor by many scientists in many lands, from Minkowski in 1892 to Banting in 1922, before insulin was consummated. Meanwhile we must work with what we have. It is hoped, in the attempt to evaluate what we have to work with, that the writer has displayed neither ignorant credulity nor cynical intolerance. In endocrinology we have had too much of both.

THE DIAGNOSIS AND TREATMENT OF HYPO-OVARIANISM*

K. G. HANCHER, M.SC., M.D., and JOHN ROGERS, M.D.

NEW YORK

Occasionally, "ovarian" feeding seems to produce truly wonderful results. They are wonderful to the patient because she has usually learned the futility of all other remedies, and wonderful to the physician because he cannot explain how the treatment acts, nor how so many apparently unrelated conditions can be favorably affected by the same agent. Nevertheless, experience apparently shows, as illustrated in the case histories narrated below, that such widely differing disturbances as constant and severe headache, or a psychosis, or high arterial tension with its annoying or dangerous complications, or a very troublesome constipation, may each be entirely relieved by this peculiar and almost incomprehensible form of organ therapy. In other words, the symptoms of a possible ovarian deficiency are so often obscured by neuroses which give no suggestion of the primary disorder that there is great need of pointing out a few indications to guide the treatment. In addition to the difficulties in diagnosis in these cases, there are also the uncertainties in both the mode of administration and the character of the medicament.

The study, of which this is a brief outline, began with an investigation of the available ovarian preparations, and, because of the very practical therapeutic problems involved in double oöphorectomy, has been confined at the outset to derivatives of the entire gland substance. The possible sources from which "active material" may be obtained are, of course, the ovarian follicle with its serous fluid, the corpus luteum, and the interstitial ovarian cells. For a test to determine the comparative potency of these substances or their extracts we first employed the acceleration or retardation of the guinea pig's oestrus, as described by Stockard and Papanicolaou.†

The extracts tested were given by mouth or by injections. As a rule, injections act in a more effective but less uniform way than when given by mouth. The mouth administration, though milder in action, produces a certain stimulating effect, which is revealed by an activation of the oestrus processes. Among the different types of mouth extracts tested (neutral, alkaline, acid aqueous, alcoholic and glycerin) the glycerin type seemed to give the most uniform results. A further report on this work will be published later by Dr. Papanicolaou, who made most of the biological tests.

Because of these findings, we have employed a glycerin extract of the whole pig ovary. That particular animal was chosen because its glands contain in greatest abundance and most constantly all of the possible sources of active material. Glycerin as an extractive material presents many advantages. It is an entirely neutral medium which introduces no changes by the presence of acidity or alkalinity. It disrupts the envelopes of the cells and then takes up all of their water soluble and a considerable proportion of their lipoidal contents and includes the nucleoproteins, globulins and albumins. A glycerin extract of the thyroid, by the way, was the first substitute employed for "fresh" gland feeding, and it gave very satisfactory results, but was later abandoned because it readily decomposed. Desiccated products were then introduced, but these present many obvious disadvantages. The drying of an entire organ includes much foreign material, especially fat which, to facilitate the drying process and to prevent decomposition, is ordinarily removed. "Defatting" excludes the lipoids from the medicament and so may change its natural characteristics and alter its effects. The subsequent drying introduces the possible or probable changes produced by autolysis or putrefaction. The feeding of fresh gland tissue is generally believed to come the closest to the ideal of a true "substitution therapy." But for general use fresh glands are impracticable. The nearest approach to this method is probably a standardized glycerin extract made from as fresh material as can be obtained. For these theoretical reasons, and because it seemed to show the best results in the oestrus tests, we selected it for repeating Dixon's experiments. He has reported[*] a marked increase of "pituitrin" in the spinal fluid after the

---

* J. Physiol., 1923, 57, 129.

injection of certain ovarian derivatives. It is a difficult and complicated test, but seems quite definite. A glycerin extract of the entire fresh pig ovary is apparently very constant and potent.* Furthermore, the effects of this material, when given by mouth, were also very clear. After its intravenous injection a large amount of "pituitrin" is demonstrable in the dog's spinal fluid within fifteen or twenty minutes. After administration by a tube through the mouth into the stomach (of the anaesthetized animal) the pituitrin does not appear in the spinal fluid until after the elapse of a much longer period. But it is then demonstrable in a considerable amount.

The follicular fluid, the corpus luteum and the interstitial cells all give this reaction, but extracts of the entire gland seem to be the most active. A detailed report of this work will soon be published. It is enough at present, however, to state that a glycerin extract of the whole fresh pig ovary, when administered by mouth, not only produces a demonstrable effect upon the guinea pig's oestrus, but also produces a demonstrable amount of a material in the dog's spinal fluid which gives the reactions of pituitrin.

It is reasonable, therefore, to infer that functional activity of the ovary stimulates functional activity in at least the posterior lobe of the pituitary and, conversely, that ovarian failure might cause a pituitary deficiency. In other words, ovarian feeding, as indicated in our dogs by Dixon's test, should stimulate the activity of the pituitary.

There is, of course, little or no knowledge of the mode of action of the endocrine glands, and still less of the manner in which these organs when fed by mouth can produce their undoubted effects. The clinical results, however, need some explanation, if only to aid in the selection of the best form of the medicament. The feeding of a "fresh gland" may, after its digestion, supply that gland's active principle. It is much less probable that any desiccated product, especially after it has been defatted, can accomplish this object. It is more reasonable to believe, however, that after the passage of the ingested material through the gastrointestinal tract and the liver there enters the circulation some "activating substance" which may

* The chemical and the physiological tests required were made by Nathan F. Blau, Ph.D.

be an antecedent of the gland's active principle. This activating substance can be supposed to facilitate or promote the parent gland's nutrition by attracting to it the most needed foodstuffs. It can be imagined to functionate like an opsonin, which attaches itself to the gland's epithelial cells and conducts into them the circulating materials which they most require. It thus activates both anabolic and katabolic metabolism, and so should increase the quantity of the defective organ's product.

If the vitality of the defective epithelium is not too much impaired, the activation of its nutrition should also improve the quality of the gland's product. In the case of the thyroid, at any rate, there is a growing suspicion that the quality of its secretion may be as important as its quantity and, clinically, there are many cases of apparent hyperthyroidism which seem to be benefited and not injured by thyroid feeding. The activating substance which is supposed to enter the circulation after the ingestion of an endocrine gland, or its derivative, must also be closely related chemically to that gland's "active principle," because, both experimentally and clinically, it performs some but not all of the functions of the patient's natural product. No amount of ovarian feeding, for example, can restore the menstrual phenomena after they have once been abolished by double castration. Nevertheless, ovarian feeding in these cases can relieve many other abnormalities and actually (in dogs) seems to stimulate the pituitary.

While these experiments were in progress a number both of male and female dogs were subjected to double castration, and the simultaneous removal of one thyroid lobe. Five months later the remaining lobe was excised and found to have gained much more in its iodin content than that of the control animals, or some 200 to 300 per cent. There is thus, as is clinically quite apparent, some demonstrably close relationship between the thyroid and the ovary.

There are many experiments which show a relationship between the thyroid and the pituitary, and Evans, in his work upon tadpoles, seems to prove that it is one of mutual stimulation. The thyroid is also generally believed to vigorously increase, probably through their autonomic or parasympathetic nerve supply, both the secretory activity and the motility of

the gastrointestinal tract. In general, it apparently accelerates throughout the body all metabolic activity.

As regards the ovary, it is possible to infer, because of the storage of iodin in the thyroid after castration, that ovarian activity and so ovarian feeding with a glycerin extract promotes the normal functionation of the thyroid and, through the thyroid, the normal functionation of the gastrointestinal tract. Also, according to Dixon's test, the same conditions or treatment can promote the normal functionation of the pituitary and thus could increase peristalsis and uterine contractions. It is, therefore, quite obvious that many of the neuroses or the symptoms which seem to be the result of hypothyroidism or hypopituitarism, especially in the digestive tract, may really originate in a hypoovarianism. Fortunately, the abnormalities in the menstrual function may give the desired clue. This has to be followed by an exclusion of the other possible causes of trouble, but the final "proof of the pudding" all too often has to rest upon therapeutic experimentation.

When the thyroid is chronically underactive, the general condition is one of asthenia, accompanied by a more or less striking pallor and an obvious deficient activity of all the other organs. When this gland is overactive there is a prevalence of the opposite conditions. The extreme cases of deficient or excessive thyroid functionation are represented by cretinism, or myxedema, or by exophthalmic goitre.

The next organ to be considered is the pituitary, which, through its output of "pituitrin" into the spinal fluid and thence into the circulation, is well known to stimulate, particularly, intestinal peristalsis and uterine contractions. It may thus, clinically, have more or less to do with either constipation or profuse or perhaps irregular menstruation. The signs which may indicate chronic inactivity on the part of this gland are extremely vague, but sometimes include frontal or temporal headache. The more pronounced, or congenital, cases are supposed to result in defective general development, especially of the genitals, or, in extreme cases, the peculiar configuration known as Froelich's syndrome.

Chronic overactivity of the pituitary is believed to be represented in some forms of giant growth, especially of the face, hands and feet, as shown in acromegaly.

complaints apart from the products of a disordered imagination.

In addition to the actual pain of menstruation, the more common and distressing accompanying neuroses which may be the result of hypoovarianism include violent headache, or migraine, or dizziness, or insomnia, or gastroenteric disturbances, or pronounced exacerbations of almost any pre-existing abnormality. If the ovarian feeding relieves the dysmenorrhea, it is almost always of more or less benefit for the concomitant difficulties.

It is impossible, at present, to explain exactly the mode of action of the medicament, but experience seems to prove that its effect is at least more than psychic. Because of the relationship of this gland with the thyroid and pituitary, and because, clinically, some cases of amenorrhea or dysmenorrhea can be relieved better by feeding either of the other two organs rather than the ovary, it is legitimate and often necessary to experiment cautiously with each of these organs, or with a combination of ovary and thyroid, or of ovary and pituitary.

Functional menorrhagia and metrorrhagia, or an excessive or an irregular menstrual flow without any demonstrable organic change, because of their frequent occurrence during the menopause, are undoubtedly associated with some hypofunctionation of the ovary. But the existing knowledge of the mechanism of these abnormalities is as vague as that about dysmenorrhea. There are a few rather indefinite facts which point to an active principle in the corpus luteum, and another with a different function in the interstitial cells. Eventually, it may be found that one inhibits and the other stimulates the menstrual flow. But until these possibilities are more clearly determined, functional menorrhagia and metrorrhagia can be regarded as indications of some form of hypoovarianism. Consequently, the feeding of preparations of the whole ovary is, at least, worthy of trial.

SUMMARY

The practice of ovarian feeding for every imaginable and imaginative female complaint is very costly to the credit of the physician and to the purse of the patient, and should be restricted to conditions in which there are at least some reasonable hopes of relief. These hopes, which as yet can with diffi-

culty be dignified as definite indications, are based almost entirely upon the existence of amenorrhea or dysmenorrhea, or of menorrhagia or metrorrhagia, or only upon abnormalities in the menstrual phenomena. The most definite and reliable is amenorrhea, and for diagnostic purposes it need not be complete. Unfortunately, this symptom apparently is not always due to a primary ovarian hypofunction or hypoovarianism, but may be secondary to some systemic failure, and that is more commonly traceable to hypothyroidism than to any other one cause. Only after all other origins are excluded, and this may be possible only after cautious experimentation with thyroid feeding, can the amenorrhea be traced to hypoovarianism, and then the cessation of menstruation in itself is seldom a legitimate complaint. Indeed, the chief difficulties often appear to bear no relationship to the ovary and can only be causally connected with that gland by exclusion or by the elimination of whatever is known of other pathological physiology. The final decision has to be reached by a comparison of the few facts which have been established for the action of the pituitary and for that of the thyroid and for what may occur after double oöphorectomy.

One chief, or cardinal, symptom which points towards ovarian hypofunctionation is, then, amenorrhea. It may be complete or "incomplete," but underactivity of the entire gland should not cause an excessive menstrual flow.

Our knowledge about functional dysmenorrhea, if it can be called knowledge, is much less definite than about amenorrhea, and is based entirely upon clinical observations, and chiefly upon those instances in which relief of the pain after ovarian feeding is complete. Dysmenorrhea, unlike amenorrhea, often, if not always, itself requires treatment and is easy of recognition. But its presence in association with other neuroses which may be much more serious is of great clinical value. The local pain seems generally, though not always, dependent upon defective ovarian nutrition and hypofunctionation is therefore presumable. This can be supposed to cause defective activity on the part of the pituitary or the thyroid, and the pituitary quite definitely and the thyroid probably can receive stimulation through ovarian feeding. Just how the commoner neuroses like headache or gastrointestinal disturbances can thus be relieved is unknown. It is probably not direct, however, but

through the influence of the ovarian product upon other secretory or nutritive organs. Not infrequently there will be encountered some neurosis in which the cause seems unexplainable. But a careful history may reveal a long past period of amenorrhea or dysmenorrhea, and either of these may give the desired clue.

The reasons for combining ovarian with thyroid or pituitary feeding are quite obvious. They seem to each reinforce what little is known of the function of the other and, practically, a much better result may be obtained by a combination than by the use of ovarian feeding alone. Furthermore, too prolonged or too intensive treatment with the ovarian derivatives sometimes is followed by nausea or gastroenteric disturbances, and these are apparently prevented by a simultaneous but cautious use of thyroid.

The available "knowledge" of the subject suggests rather than proves that menorrhagia and metrorrhagia are, at least before the menopause, not regularly the direct result of hypofunctionation on the part of the ovary. During the menopause, however, menorrhagia and metrorrhagia are common, and may result from deficient ovule formation, although the results of oöphorectomy are against this possibility.

When more is known of the function of the interstitial cells, these menopause disturbances may be better explained. But until then menorrhagia and metrorrhagia can be said to be indications for ovarian feeding only during the menopause. They suggest in earlier ages a primary pituitary rather than an ovarian hypofunctionation. The best medicament for ovarian feeding at present, in our experience, is a glycerin extract of the entire fresh pig ovary.

Case. I. Mrs. R., aged 29, required in 1921 complete hysterectomy, with double oöphorectomy, for fibroids complicated by salpingitis with cystic and suppurative disease of the ovaries. On April 4, 1923, she presented herself with complaints of more or less constant and severe headache, very troublesome insomnia, marked constipation and the nervousness and frequent hot flushes of the artificially induced menopause. There had been no great gain in weight. She had been taking, without benefit, and in rather large dosage, 5 grain tablets of different ovarian preparations. Physical examination was negative. The pulse rate was 72; the systolic blood pressure, 115; metabolism and urine, normal. She was given the 10 minim pills of the glycerin extract of fresh pig ovary to take three or four times daily.
Ten days later, this patient professed to have been relieved of the

headache and much of the insomnia, but found that four of the glycerin extract of ovary pills produced anorexia and nausea. The dosage was then reduced to two or three pills daily. This seemed to improve the constipation. On June 9, 1923, all symptoms had disappeared and there were no complaints. There was no headache, no indigestion nor insomnia, and the bowels moved without the need of laxatives.

The headaches and insomnia began soon after hysterectomy and oöphorectomy, and had persisted in spite of the usual ovarian feeding until she had begun to take the glycerin extract of fresh pig ovary. After that was given the improvement had been rather gradual, but after two or three months all the abnormal symptoms had slowly disappeared.

At present, June, 1924, under this medicament the condition remains normal with an occasional slight headache, but more than ten to twenty minims daily of the glycerin ovarian extract has been found to induce nausea. In this case the symptoms were almost entirely subjective, but there can be little doubt of the marked improvement which could not be effected by any other means.

Case II. Mrs. C. H., aged 34, suffered from dysmenorrhea from the beginning of menstruation. When 19 she was "dilated" and curetted and wore a glass-stem pessary without relief. She married at 22 and became pregnant, but lost the child in a difficult labor followed by infection which required the removal of one tube and ovary. Two years later, a ruptured extra-uterine pregnancy with infection required another operation and the removal of the other tube and ovary. Following this, for the last five years there has been, of course, complete amenorrhea. With this there were the usual symptoms of the artificially induced menopause, but of considerable severity. For the past two or three years there has been noted a slight "goitre" (perceptible simple hypertrophy). The present complaints are those of weakness, coupled with a steady gain in weight; gaseous indigestion, constipation and troublesome insomnia. But more distressing than anything else, there is constant headache, chiefly in the temporal region. On physical examination, there were found the old laparotomy scars, a good color and a good general nutrition, but flabby musculature. There was a slight soft thyroid enlargement. The pulse rate was 76; systolic blood pressure, 250; weight, 146 lbs.; height, 5 ft. 6 in. Urine and blood examination were negative. She had taken "all kinds of treatment," especially different forms of ovarian feeding, but in spite of everything that had been done, the headache, blood pressure and gain in weight had steadily though slowly increased.

On February 6, 1923, she was given a 10 minim pill of the glycerin extract of fresh pig ovary to take four times daily.

On March 29, 1923, there was noted a marked improvement in the headache and strength, and some loss of flesh. The systolic blood pressure was 220, the weight 140. The 5% thyroid nucleoprotein tablets were then substituted for the glycerin extract of ovary.

On May 10, 1923, many of the former symptoms had returned, and the weight had increased to 150 lbs. The systolic blood pressure remained at 220. Glycerin extract of fresh pig ovary in 10 minim pills four times daily was then resumed.

On June 6, 1923, she reported that she had been freed of headaches soon after taking the ovarian pills. The systolic blood pressure had fallen to 170, and the weight to 148 lbs.

There were still some evidences of hyperthyroidism in the soft, slightly enlarged thyroid, the pallor, the weakness and defective gastrointestinal activity; consequently, she was given the 10 minim

pills of the glycerin extract of thyroid in conjunction with the glycerin extract of pig ovary.

On November 22, 1923, she reported that she felt very well, but . . . . of the ovarian feeding caused a recurrence of the . . . . —as omitted there was defective energy and gaseous · · . · systolic blood pressure was then found to be 160 and the weight had decreased to 132 lbs. The thyroid enlargement had disappeared.

Since then she writes that the ovarian feeding has to be continued daily, but a little thyroid seems necessary to maintain her full strength and to prevent a tendency to become stout.

This case, though a little confused by the addition of thyroid to ovarian feeding, is clearly from the time of operation for the extra-uterine pregnancy, one of ovarian deficiency, and a less pronounced primary or former deficiency might be inferred from the dysmenorrhea which had existed from the outset of menstruation. Following the loss of the ovaries, there were the usual menopause symptoms and, in addition, the development of the headaches, the rising blood pressure and the increase in weight. That the blood pressure could be reduced by feeding glycerin extract of fresh pig ovary and not by any of the other ovarian products which had been given was quite evident. The coincident simple hypertrophy of the thyroid is suggestive of the thyroid-ovarian relationship; also, that the hypertrophy disappeared after thyroid and ovarian feeding. But the chief point is that the steadily rising blood pressure and alteration in general health was apparently stopped by ovarian feeding. That organ, in this particular instance, at any rate, might be called one that was essential for life. A blood pressure of 250 in a woman of 34 could not very long remain at that point without being followed by irreparable vasculo-cardiorenal disorders.

Case III. Miss D. W., aged 48, had the right lobe and isthmus of the thyroid removed in 1906 for hyperthyroidism. Complete recovery followed. In 1910 and 1914 there were mild signs of hypothyroidism, which were relieved by feeding thyroid nucleoprotein material. In July, 1923, she went to the country and the expected menstruation did not occur, and later the amenorrhea persisted. Very troublesome insomnia soon developed, and was accompanied by great nervous irritability and some mild delusions. She was then given by the local physician some tablets of corpus luteum and afterwards of *desiccated whole ovary, but with negative results.* The mental disturbance grew gradually worse, with pronounced hallucinations of sight and hearing. She was brought back to the city in September in a rather emaciated condition, and the disturbance then appeared to be a psychosis of the menopause with delusions of persecution. There was no other gross abnormality, except a slightly elevated blood pressure. The abdominal examination was negative, but on account of the four months of amenorrhea and mental condition no vaginal examination was attempted. She remained at her home under the care of a sister, and was given four times daily the 10 minim pills of glycerin extract of the pig ovary.

During the next three weeks the psychosis gradually grew less troublesome, and on October 11th menstruation appeared. After it had continued three weeks and was profuse, a vaginal examination revealed a fibroid uterus which could only with difficulty be palpated above the symphisis. As the menstrual flow was not excessive, and the psychosis was evidently improving, operation was deferred until the mental condition seemed normal. No peculiarities, except the bloody vaginal discharge, were noted after the middle of December, and on December 29, 1923, with considerable difficulty, the fibroid,

which was tightly wedged in the pelvis, was removed by supravaginal hysterectomy. Both ovaries were left in place. The left contained a corpus luteum. An uneventful convalescence followed, and as the psychosis had entirely disappeared, the glycerin extract of fresh pig ovary was discontinued. This patient was seen in June, 1924, and appeared perfectly normal.

The interesting points in this history are the amenorrhea and the following psychosis, neither of which was affected by the administration of the ordinary desiccated ovarian products. But after the administration of glycerin extract of fresh pig ovary the psychosis began to improve, and shortly afterwards the menstrual flow appeared. Its persistence led to the discovery of the hitherto unsuspected fibroid tumor of the uterus. The removal of the latter, after the mental condition had become normal, apparently because of the ovarian feeding, did not cause any recurrence of the psychosis.

Case IV. Miss E. B., aged 20, was first seen in February, 1921. She gave a history of dysmenorrhea accompanied by severe headache since the inception of menstruation at the age of 13. In 1916, the appendix was removed, but dysmenorrhea, especially on the right side, became worse. Early in 1919, the right tube and ovary were excised, apparently to relieve the pain. A few months later the left tube and ovary were removed to relieve the continued dysmenorrhea and "adhesions." Later the tonsils were excised. Following the double oöphorectomy constipation became excessive, and another laparotomy was performed for "adhesions," but without relief. After all these operations a slight "goitre" appeared and tachycardia became troublesome. In February, 1921, she presented the picture of typical, rather severe, exophthalmic goitre, but with obstinate constipation. The bowels could be moved only by prolonged daily irrigations.

Palliative treatment by iodin and adrenal feeding was tried for nearly a year, at first with some benefit, but later without gain.

In March, 1922, all four thyroid vessels were tied in two sittings under local anesthesia. Then the iodin and adrenal feeding produced a slow but steady improvement. In September, 1922, the Graves' disease seemed cured. The exophthalmos and goitre had disappeared; the pulse was 80, but the systolic blood pressure was normal had risen to 145. The constipation was unchanged. "Hot flushes" and general nervous irritability were the other chief complaints. The glycerin extract of fresh pig ovary was then used for the first time.

In March, 1923, she reported that ovarian feeding relieved practically all of the distress except the constipation. She had lately been vigorously indulging in social pleasures, with dancing and late hours, and in April the tachycardia reappeared, and she needed treatment of the thyroid with x-ray. This, with rest, reduced the pulse rate to normal again in about one month. If feeding with the glycerin extract of fresh pig ovary was suspended, however, the "nervous irritability" and hot flushings returned. There was still very obstinate constipation, and the systolic blood pressure was 170.

In February, 1924, anorexia and nausea and then vomiting after each meal began. This gradually grew worse in spite of every kind of treatment, including rest in bed, sedatives, rectal feeding and gastric lavage. In June she was brought to the hospital again. The weight had decreased from 120 lbs. in February to 88 lbs. The pulse was 70; blood pressure, 140; there were no signs of thyroid disease; the urine was negative except for acetone. Fluoroscopic examination of the stomach (by Dr. A. L. Holland) was accomplished with some difficulty, but revealed no appreciable abnormality. The diagnosis

was nervous or hysterical vomiting. Nothing could be retained for more than a few minutes before entering the hospital. During the first three days there was a loss of weight of 2 lbs, and the acetone in the urine increased. Feeding by a duodenal tube was then instituted, and the glycerin extract of whole fresh pig ovary was added to the food; the vomiting promptly stopped. The tube was very irksome to the patient, and after four or five days first water, and then liquid foods were given by mouth, at first with the tube in place, and the vomiting did not recur.

This case is chiefly interesting because of the apparent causal relationship of the loss of the ovaries to the subsequent very serious developments. I have never before seen what seemed to be a pure hysteria threaten to come to a fatal ending. The patient through it all was calm (and in the hospital separated from• sympathetic relatives), and evidently tried to help herself. Was the hyperirritability of the stomach really hysteria, or some neurosis of the stomach for which as yet there is no explanation?

This case has again relapsed and is again being treated with ovarian feeding and seems again improving.

CLINICAL SIGNIFICANCE OF THE CONGENITAL ABSENCE OF THE UPPER LATERAL INCISOR TEETH*

HOMER WHEELON, M.D., F.A.C.P.
SEATTLE, WASHINGTON

Information is extremely limited concerning the significance of the congenital absence of the upper lateral incisor teeth. In spite of the limited information, opinions as to the causation and meaning of this condition are markedly divergent. Partly because of this lack of unanimity of opinion and partly because of the paucity of information, I have deemed the subject of sufficient general interest to warrant a presentation of the clinical findings of one patient in whom the upper lateral incisors are definitely deformed and three in whom the upper lateral incisors of the second dentition never appeared, and in whom radiographic examinations failed to reveal the presence of unerupted teeth.

PRESENTATION OF CASES

Case No. I. Sept. 17, 1924. Mrs. G. M., aged 27 years, white, attorney.

Complaints. Upper abdominal distress, lassitude, nervousness and chronic bronchorrhea were present.

Family history. The maternal grandmother, her oldest daughter, mother of the patient, and two youngest sons are subject to severe attacks of migraine. The patient's two sisters have very irregular teeth, although the upper lateral incisors are in position. Both the mother and maternal grandmother have been irregular in the menstrual periods. Two maternal uncles have suffered from nervous breakdown. One uncle recovered his health at the age of thirty years; the other has remained melancholic. He has four children, all of whom show marked dental anomalies.

Clinical history. The patient weighed 8½ pounds at birth. She was breast fed for a short time. There was considerable gastrointestinal trouble following the establishment of artificial feeding. On two occasions she had convulsions, which were considered the result of gastric disturbances. She was a fat baby and has always been overweight for her age and height. The present height of 60½ inches was attained at the age of 14 years.

Infantile eczema was an annoying condition during early life. She had measles when a child, and contracted mumps at the age of 14 years. Fever and chills (malaria) were common occurrences

between the ages of 6 and 13 years—"I would go to school in the morning feeling fine, and be carried home in the afternoon with a fever."

The patient had a severe attack of sinusitis and many irrigations of the antrums about her 14th year. A second attack of sinusitis in 1921 was followed by an attack of severe vesicular dermatitis which ran a course of 14 weeks. A distressing catarrhal condition of the nose and throat and also persistent cough and bronchorrhea have been present since an attack of whooping cough at the age of 4 years. She has had two attacks of pleurisy without effusion. For these conditions she has had a great deal of local and general treatment, including the use of autogenous vaccines. At the age of 21 years she contracted pulmonary influenza, from which she "did not recover for months" and which left her respiratory tract "greatly weakened." She has been and continues to be sensitive to climatic changes and is prone to colds. The respiratory condition becomes much improved while in a dry, clear climate. The tonsils have been "removed on three occasions." She is subject to attacks of hay fever and asthma. Positive skin reactions have been obtained with cat hair and rose pollen antigens.

The skin has always been sensitive. Slight contusions cause marked discoloration, and irritation results in extensive "scaldings."

Menstruation was established at the age of 12 years and 3 months. The periods have never been regular. The time variation between periods has been from 2 months to 2 years. The menstrual flow, when established, usually lasts about 5 days and is not associated with headache, nausea or pelvic cramps. She was married at the age of 25 years but has never been pregnant.

The pulse for years has averaged around 60 per minute while quiet. Her normal temperature is 97.4 F. The basal metabolic rate a year ago was —9 per cent. She has received thyroid preparations with benefit.

She has led a rather active physical and social life. She is now engaged in the practice of law. She is very emotional, energetic and forceful. Only of late has weeping appeared in her emotional life.

Present status. For nearly a month she has noted an unnatural nervousness and just lately a diminution of the appetite—"an entirely new symptoms"—lassitude and a vague sense of depression. The loss of appetite has been associated with a vague, full, dragging distress in the upper abdominal region and slight nausea and aversion to food. The bowels are regular. There has been nocturia and frequent urination of late; however, urination has not been difficult or associated with distress of any sort. Her sleep is less sound and refreshing than formerly. She complains of being tired in the morning and again at about 3 p. m. "I feel hectic and all worn out." The emotions are less stable than formerly; she resents being alone. There are periods in which she experiences a sense of "internal emotions" which are not associated with tremors. These periods are usually followed by mild depression which is characterized by worry. There is a slight low backache. She has a persistent productive cough which is most marked in the morning. She does not complain of dizziness, night sweats, muscle cramps or joint pains. She has not menstruated for several months. Sexual desire is strong; however, there is delay in culminating the sexual act.

Physical examinations. The patient is of short stature and appears to be considerably over weight. There is marked fat padding

about the hips and over the shoulder girdle. The hands and feet are very small. The fingers are short and tapering.

Weight	68.6 K.	151	pounds
Height	152.5 cm.	60	inches
Torso	76.5 cm.	30⅛	inches
Lower	76.0 cm.	29⅞	inches
Span	142.0 cm.	55⅞	inches
Neck circumference	33.5 cm.	13¼	inches
Shoulder circumference	95.0 cm.	37½	inches
Axillary circumference	81.0 cm.	31⅞	inches
Abdominal circumference (at navel)	68.0 cm.	26⅞	inches
Trochanteric circumference	90.0 cm.	35½	inches
Head circumference (above ears)	54.0 cm.	21¼	inches
Head circumference (over vertex)	34.5 cm.	13⅝	inches
Interpupillary distance	5.8 cm.	2¼	inches

The skin is smooth, moist and cool. The hands and feet are cold to the touch. The head hair is abundant, coarse, very bushy and has a moderately high anterior attachment. The eyebrows and lashes are well formed; there is no nasal brow. The axillary and pubic hair is normal in amount and distribution. There is a growth of fine hair on the upper lip. The finger nails are smooth and brittle; the lunulae do not show.

The blood pressure is 112/64. The buccal temperature is 98.6 F. (usual normal, 97.4 F.). The pulse is 76 per minute (normal about 65), regular and of good quality. The heart sounds are regular. There are no cardiac murmurs. There is a cough which is productive of foul-smelling sputum. There are coarse bubbling rales over the midportions of the chest. Diaphragmatic movements are free and full. The vital capacity of the lungs is 2.6 liters.

There are small remnants of lymphoid tissue in the tonsillar fauces. The sinuses are clear upon transillumination. The mucosa of the nose and pharynx is quite reddened. The voice is rather low pitched. The tongue is clear and free from fissures or indentures. The palatal arch is moderately high. The dental ridge is quite wide. The upper central incisor teeth are very large and spaced (Fig. 1). The upper lateral incisor teeth are small and peg-like. There are numerous small white opaque spots in the teeth.

The basal metabolic rate is —2 per cent. The isthmus of the thyroid glands is not palpable.

Deep pressure over the upper abdominal region causes but little distress.

A gynecological examination made one year ago "was entirely negative." Vaginal smears show the presence of numerous pus cells, bacteria and epithelial cells.

The reflexes are all present and equal on the two sides. The knee jerks are very active.

Radiographic examinations. The heart and aorta are negative. The hilus shadows are considerably thickened and contain many calcareous areas. There is considerable generalized parenchymal infiltration radiating from the hilii. The apices and bases of the lungs are clear. Movements of the diaphragm are unobstructed.

The clinoid processes are large and nearly bridge over the sella. The floor of the sella is not definite in outline or position. The right mastoid cells are quite dense.

The bones of the hand and wrist are all present and of rather small size; the epiphyses are all closed.

cells in the voided specimen. Occasional pus cells are present in the catheterized specimen.

Diagnoses. The case is diagnosed as follows: present ailment, entero-pulmonic La Grippe or influenza; general diagnosis, hypofunction of the pituitary, thyroid and gonads.

Case No. II. Aug. 29, 1923. Miss N., aged 28 years, white, accountant.

Complaints. Convulsive seizures during the night, rapid increase in weight and urticaria during the fruit season were the outstanding symptoms.

Family history. See Fig. 2.

Clinical history. The patient has been continually over weight since birth. The deciduous teeth had to be extracted and the gums lanced to permit eruption of the permanent teeth. The right upper lateral incisor never appeared and repeated radiographic examinaitons have not shown an unerupted tooth. She contracted scarlet fever at the age of four years, from which she made an uneventful recovery. She was free from fits or convulsions as a child.

Figure 2. Genealogy of Case No. II.
I. 2. Died before the age of 30 years. 4. Congenital absence of the right upper lateral incisor tooth; no convulsions.
II. 1 and 2. Died of pulmonary tuberculosis. 3. Normal teeth; slender build; a large goiter. 4. Congenital absence of the right upper lateral incisor tooth; no convulsions.
III. 1. Congenital absence of the right upper lateral incisor tooth; no convulsions. 3. Congenital absence of the right upper lateral tooth; died following appendectomy. 4. Patient: Congenital absence of the right upper lateral incisor tooth; prognathism; nocturnal convulsions. 5. All teeth present; irregular menstruation; nervous; goiter. 6. Congenital absence of the left upper lateral incisor tooth; no convulsions. 8. Congenital absence of the right upper lateral incisor tooth. 9. Congenital absence of the right upper lateral incisor tooth; prognathism.
IV. 2. Congenital absence of the right upper lateral incisor tooth.

Bodily changes were not marked at the adolescent period. Menstruation was established at the age of fourteen years. The initial flow lasted five days. The periods occurred every twenty-eight days and were not associated with pelvic cramps, backache or headache. There was complete cessation of menstruation for a period of six months, following a fall into a river during a menstrual period, during her twenty-third year.

At the age of eighteen years the patient was thrown from a horse and sustained back and head injuries. She was unconscious for a few

minutes and bled freely from the nose. Two days were spent in bed and apparently she recovered completely from the accident.

The patient finished high school and took work at the university. She is now an accountant and successful in her work.

Present status. Four years ago the patient had a nocturnal convulsion which lasted but a few moments and which did not arouse her (convulsion witnessed by her mother). At that time her physician diagnosed her condition as the result of constipation. One year later she experienced a second convulsion and continued to have an attack each month for about six months. The last attack occurred in August, 1923, one year having intervened since the preceding attack. Convulsive seizures have never occurred during the day, or while awake. At no time have the seizures been associated with frothing at the mouth, loss of sphincter control or muscle soreness. The attacks are usually followed the next day by a severe frontal headache. On several occasions she has noticed dark spots in front of the eyes during the day preceding an attack. The patient thinks "that a full meal or extreme fatigue predisposes to an attack." The seizures have no relation to the menstrual period.

There is no stomach trouble. A considerable amount of fluid is taken each day. She craves and eats much starch and sugar. She suffers considerably with hives during the fruit season. The bowels are very inactive. For three years she has used cathartics daily— "I would go six days without a bowel movement if I did not take something." Throbbing frontal headaches occur as the result of constipation and are quickly relieved by a free bowel movement. She complains of bitemporal throbbing when she lies down. Glasses are worn. The menstrual periods are regular and free from distress. There has been a continual, steady gain in weight for the past three years—130 to 162 pounds. The fat is deposited mainly over the trunk and abdomen.

The patient is good-natured, keen to her surroundings and is "far from being temperamental."

Physical examination. There is marked fat padding, especially of the shoulders, upper arms, and about the hips. The breasts are pendulous and free from masses.

Weight	72.3 K.	159	pounds
Height	157.5 cm.	62¼	inches
Length of legs	84.0 cm.	33⅛	inches
Length of torso	73.5 cm.	29	inches
Spread of arms	166.5 cm.	65¾	inches
Circumference over shoulders	104.0 cm.	41	inches
Axillary circumference	95.0 cm.	37½	inches
Circumference of bust	105.0 cm.	41½	inches
Circumference at navel	90.0 cm.	35½	inches
Circumference over trochanters	110.0 cm.	43⅜	inches

The skin has an excellent color and is soft, moist and pliable. The hair of the head is abundant, lustrous, brown in color, of very fine texture and has a high anterior attachment. The eyebrows and lashes are well formed. Axillary and pubic hair is normal in amount and distribution. Hair is absent from the face and over the body save for a delicate growth on the forearms and legs. The nails are firm and smooth.

The tonsillar fauces are empty. The voice is clear and well modulated. The teeth are of moderate size, well spaced and of a clear bluish tint. The right upper lateral incisor tooth is absent. There are several devitalized teeth. The palatal arch is moderately high. The tongue is clear and free from markings.

Cervical glands are palpable along the left side of the neck. The

thyroid gland is not palpable. The basal metabolic rate is +1 per cent.

The heart, lungs, genitalia and rectum are negative. The reflexes are all present and equal on the two sides. Possibly the knee jerks are somewhat exaggerated. The blood pressure is 122/75. The pulse is 74 per minute and the temperature 98.2 F.

X-ray examinations. The heart is normal as to position, size and shape. There is no evidence of a persistent thymus gland. The diaphragm moves freely. The hilus shadows are moderately prominent.

The esophagus and stomach are negative. The duodenal cap fills evenly. Barium is retained at the inferior flexure of the duodenum. Reverse movements of barium in the duodenum occur frequently, although such movements are not associated with belching or nausea. This condition was most pronounced at a time when the colon was filled with barium from the preceding day's meal.

The cecum lies low and is not freely movable. The appendix was not visualized during the three days examination. The colon is especially spastic at the splenic flexure and throughout the descending portion. The colon and stomach are held well up in the abdomen. There are no points of tenderness or rigidity over the abdomen or pelvis.

Radiograms of the lateral head do not show changes about the sella turcica, although the sella is rather deep. The sinuses are of moderate size and clear. The epiphyses of the hand are closed.

Laboratory examinations. The Wassermann test is negative with cholesterinized antigen and the Noguchi modification, and positive 1 + to the ice box method with cholesterinized and Kolmer's antigens. The hemaglobin is 88 per cent (Dare). The red cell count is 5,456,000 and the white count 11,000 following the noon meal. The differential count shows neutrophiles, 53; small lymphocytes, 29; large lymphocytes, 13; eosinophiles, 2; transitional cells, 3.

The urine, on two occasions, showed faint traces of albumin.

Diagnosis. The patient has chronic appendicitis, allergy, hypophyseal obesity and petit mal (nocturnal) epilepsy.

Case No. III. May 18, 1923. Mr. F. E. S., aged 34 years, white, mechanic.

Complaints. There are pains about the heart upon taking a deep breath, shortness of breath, nervousness, cardiac distress when under moderate stress, backache for over four years which has incapacitated him for hard work, and night sweats for three weeks. He also complains of severe dizziness and frontal headache.

Family history. See Fig. 3.

Clinical history. The patient weighed 13½ pounds at birth. He was walking and talking at about twelve months. He was plump until the age of nine, at which time he began to grow rapidly in height. At the age of thirteen years he attained his present height. He now wears the same size shoe, hat and glove that he did at the age of thirteen years. At thirteen he wore a number thirty-six coat; he now wears a number forty.

He had mumps before the age of seven years. He had three attacks of measles, an attack of diphtheria, scarlet fever, typhoid-pneumonia at the age of nineteen years and pulmonary influenza at the age of thirty years. He has had blood poisoning on three occasions following local infections of the extremities.

At the age of eleven years he was kicked in the left parietal region of the head. The blow rendered him unconscious for a "considerable time" and was followed by immediate hemorrhages from the nose, ears, eyes and mouth. The nasal hemorrhage was not checked

until the third day. "I was bled white before they stopped the hemorrhage." Following this injury, the patient claims that he experienced daily hemorrhage from the nose—occasionally as many as thirteen a day—until the age of thirty-one' years. Any sudden movement of the head, or moderate bodily strain was sufficient to incite a nasal hemorrhage. At the age of twenty-six years he was thrown from the roof of a street car, but managed to alight on his feet. There was no immediate disturbance following the fall; however,

Genealogy of Case No III.

Paternal

II. 1 Physician 73 years old when first child was born to him by his first wife Two sons and two daughters were born to him by his second wife, who married him at the age of 55 years

III. 2 Male children either aborted or died in spasms immediately after birth 3 Marked spacing of the upper teeth; height 5 feet, 11½ inches, weighed 140 pounds at 25 years of age and 280 pounds at the age of 57 years Wife had congenital absence of the upper lateral incisor teeth 4 Nurse: died of cancer of the stomach.

IV. 10 Wt 8 pounds at birth; teeth markedly spaced, congenital absence of the left upper lateral incisor tooth A daughter shows congenital absence of the left upper lateral incisor tooth P Patient· Wife has diabetes mellitus she has conceived 5 times and has brought only the first and last child to term, the other three were aborted before the 5th month of gestation The first child was delivered at 8 months and lived 7 days, the fifth child was delivered two weeks over-time, weighed 12½ pounds and died within two weeks 12 All teeth present, weighed 12 pounds at birth, drowned 13 Drowned.

Maternal

I 1 Congenital absence of the upper lateral incisor teeth; husband's teeth "perfect."

II 1 Died of Bright's disease at the age of 51 years; full set of teeth 2 Congenital absence of the upper lateral incisor teeth; Bright's disease 3 Congenital absence of the upper lateral incisor teeth; sugar in urine during latter part of life 4 Congenital absence of the upper lateral incisor teeth; Bright's disease 5 Teeth irregular and crowded; Bright's disease 6 One of twins Congenital absence of the upper lateral incisor teeth, operated upon at the age of 21 years for the removal of gall stones, mentally unbalanced, kidney trouble 7. One of twins Died in spasms while very young 8 Congenital absence of the right upper lateral incisor tooth 9 "Teeth normal."

III 1 Spacing of upper teeth 10 Congenital absence of the left upper lateral incisor tooth A daughter has a similar dental anomaly

Wife

I 1 Died at the age of 96 years sugar in the urine during latter years. 2 Second wife, living at 62 years of age, blind, sugar in the urine for several years

II 1 Died at the age of 39 years of diabetes mellitus 8, 9 and 10. Died of diabetes mellitus

III 1 Died at 3 months from sun stroke 2 Eczema and diabetes mellitus, operation (1924) for congenital cystic endometritis 3 Died in diabetic coma 1924 4 Eczema, died at the age of 23 years of diabetes mellitus when 6 months pregnant 5. Diabetes mellitus and an ovarian mass 6 Eczema, died in infancy. 7 Diabetes mellitus; very nervous

IV 1 Menstruation at the age of 15 years; pulmonary tuberculosis during adolescent period 2 Backward in school 3 Died at 8 months because of "pressure on the spine" 4 Eczema and nervousness. 5 Nervous 7 "Died of jaundice" at one week of age 8 Lived 20 minutes 9 Died at birth 8 and 9 were "swollen blue babies" 10 Lived two weeks 11, 12, 13 Miscarriages 14 Died shortly after birth

five days later he developed a severe backache which confined him to his bed for a week. Since the fall his back has remained weak and at times has incapacitated him for work. He states that his back has never been strong since the age of five years, at which time he jumped to the ground from a second-story window. There have been several light attacks of cystitis.

Adolescence appeared at the age of thirteen years; the voice changed and libido appeared. He states that since the age of thir-

teen he has been excessively passionate sexually and that he has over-indulged in venery ("Intercourse six to nine times in one night for as much as five nights running"). He denies having ever had a chancre or gonorrhea. He married at the age of twenty-five and was the father of five children, all of whom died either before, at, or soon after birth.

The patient finished the grade schools and spent two years at business college.

Since early youth, the patient has been subject to deep emotional depression and melancholia; however, he has never entertained the

Figure 3

idea of suicide. He is not sociable, preferring to be alone and quiet. Excitement of any kind is distressing because it causes him to "flush and shake." He is quick tempered and subject to fits of anger in which he entirely loses self-control. "I go insane and blind and don't know what I am doing or saying." He states that his mother had a similar disposition. On three occasions he has nearly choked a man to death because of his unreasoning rage. Following such outbursts of emotion, he becomes remorseful and depressed. There has been no evidence of paranoia; however, he holds a grudge with con-siderable tenacity and forgives with difficulty.

Alcohol has been used in moderate amounts; tobacco excessively. He drinks from six to eight cups of coffee a day.

Present status. There has been a great deal of throbbing headache and dizziness for the last few months. There is a sense of extreme lassitude and physical inability. Moderate effort is followed by cardiac distress and dyspnea. There is a great deal of pain in the lumbar region and some in the neck. For several months he has been getting gradually more nervous and irritable. Libido has gradually become reduced.

Physical examination.

Height .... 168.0 cm.   66¼ inches
Weight .... 60.5 K.   133   pounds

There is a marked anemic pallor of the skin. The temperature is 98.0 F.; the pulse, 92; the blood pressure, 165/115. The tonsils are large and markedly infected. The urine is free from sugar, pus cells and casts; there is a faint trace of albumin. Radiograms of the teeth revealed the presence of four periapical abscesses; there is marked pyorrhea. The teeth are markedly spaced. The upper lateral incisors are absent and radiograms fail to show the presence of unerrupted teeth (Fig. 4).

Figure 4. Photograph of the dental apparatus of Case No. III. Note the marked spacing and absence of the upper lateral incisor teeth.

The patient was advised to have his teeth attended to and his tonsils removed. The teeth were extracted with marked improvement in his condition.

The patient returned September 9, 1924, complaining of tiredness and weakness in the morning and persistence of the backache. Since his previous visit there have occurred two persistent spots before the

left eye of which he is continually conscious. He has been free from dizziness for the past six months and headache for three months. The night sweats ceased soon after extraction of the teeth.

Second physical examination.

Weight	65.5 K.	144 pounds
Height	168.0 cm.	66¼ inches
Leg length	88.0 cm.	34¾ inches
Torso length	80.0 cm.	31⅝ inches
Span of arms.....................	177.0 cm.	69¾ inches
Circumference over shoulders.......	108.0 cm.	42⅝ inches
Chest:		
Expiration	86.0 cm.	33⅞ inches
Inspiration	93.5 cm.	37 inches
Circumference at navel............	81.0 cm.	32 inches
Circumference over trochanters.....	88.0 cm.	31⅝ inches
Circumference of head above ears...	55.0 cm.	21¾ inches
Circumference of head over vertex..	35.5 cm.	14 inches
Interpupillary distance............	5.5 cm.	2¼ inches

The blood pressure is 190/98; the pulse, 90; and the buccal temperature, 98.8 F.

The skin is moist, has a normal color and "perspires freely." The head hair is straight, dark and has a moderately high anterior attachment. The eyebrows are well formed and there is no nasal brow. The axillary and pubic hair is abundant and of normal distribution. There is a moderate growth of hair over the chest, forearms and legs. The finger nails are hard and smooth. There is moderate acne over the back.

The tonsils contain a small amount of pus. The tongue is clear. Anterior cervical glands are just palpable on both sides of the neck. The sinuses are clear upon transillumination. The isthmus of the thyroid gland is barely palpable.

The chest is negative to auscultation, percussion and fluoroscopy. The diaphragm moves freely. There is definite left heart preponderance. The first aortic sound is slightly roughened and the second snappy.

The abdomen is negative to physical examination. The testes are firm. The right inguinal ring easily admits one finger. There are several small hemorrhoids which bleed easily. The prostate gland is of moderate size and not hard. There is some slight inflammation about the anus and over the perineum, puritus ani. The arches of the feet are quite high.

All reflexes are present and equal on the two sides. The knee jerks are very active. There is no Rombergism nor evidence of tremors.

There is some tenderness upon deep pressure over the upper lumbar spine. The curve of the spinal column is normal. The scapular borders show only moderate concavity.

Radiographic examinations. The lungs are clear save for a slight increase in the density of the hilus shadows. The domes of the diaphragm are smooth; diaphragmatic movements are normal. There is moderate hypertrophy of the left ventricle. The mediastinum is negative.

The plate of the lateral head shows the skull to be of uneven thickness. The occipital protuberance is very prominent. The sella turcica is large. The clinoid processes are prominent. The mastoid cells are extensive and clear.

The osseous structures of the pelvis are normal. The sacral joint does not show pathological changes.

Laboratory examinations. The urine has a specific gravity of 1006 and an acid reaction. Occasional pus cells and a faint trace of

albumin are present in the urine. The kidney function test shows a 50 per cent return of the dye in two hours and fifteen minutes. There was a total secretion of urine of 1020 cc. during the test period. The cystoscopic examination is entirely negative.

The Wassermann reaction is negative. The hemoglobin is 101 per cent (Dare). Cell counts show: 5,568,000 erythrocytes; 8500 white cells. The differential count shows: neutrophiles 71; lymphocytes 7; large mononuclears 21; and eosinophiles 1.

Diagnoses. The case is diagnosed as follows: present ailment hypertension and mild tonsilitis; general diagnosis, anterior lobe hyperpituitarism.

Case No. IV. Aug. 13, 1923. Miss F. S., age 15 years, white, student.

Complaints. There is a constant productive cough, profuse expectoration and malnutrition.

Family history. The mother has been operated upon for cancer of the breast and a ruptured appendix. She is of short stature and slight build; her two sisters are "above the average height." The father is living and has a marked anemic pallor. He was short and very fat until his seventeenth year, following which he "shot up all at once and became quite thin." The one sister is feeble-minded and is a typical case of dystrophy adiposogenitalis. The mother, sister, father and two maternal aunts have normal upper later incisor teeth.

Clinical history. The patient weighed ten pounds at birth and continued over weight until the age of two years. She was speaking a few words at twelve months. She suffered a severe attack of thrush during her second year; this lasted three months. Ten of the deciduous teeth were lost during this attack of thrush. She has had measles, chicken-pox and pulmonary influenza. At 11 years of age she contracted whooping-cough, from which time there has been present pulmonary distress, cough and profuse expectoration. She is subject to colds.

The permanent teeth were slow in erupting and were irregularly spaced. The upper lateral incisor teeth have never appeared. Glasses have been worn since the age of seven years because of diminished vision, myopia and right eye squint. Growth was slow and continued until her fourteenth year.

Menstruation was established late in her fifteenth year. The initial flow lasted nine days. Nausea and back pains were experienced the day preceding the flow.

She finished grammar school at the age of fifteen years.

Present status. The appetite is good and the bowels are regular. Sleep is sound and refreshing. There is no nocturia or distress upon urination. There is a deep, harsh cough which is productive of large quantities of foul-smelling muco-purulent matter.

There is no complaint of headache, dizziness, nausea, muscle or joint pains, lassitude or emotionalism. She is energetic, sociable and serious minded.

Physical examinations. The patient is under-nourished, of small stature and poor posture. The shoulders are stooped and the sternum sunken.

Weight	42.7 K.	94	pounds
Height	154.5 cm.	61	inches
Torso	77.5 cm.	30½	inches
Lower	77.0 cm.	30¾	inches
Spread of arms	156.0 cm.	61⅝	inches
Circumference over shoulders	88.7 cm.	35	inches
Circumference at umbilicus	65.0 cm.	25⅝	inches
Circumference over trochanters	80.0 cm.	31⅝	inches

The skin is rough and mottled. The hands and feet are livid and cold to the touch. The cheeks are markedly flushed. There are numerous small moles over the right side of the face. The head hair is fairly abundant, of fine texture and has a high anterior attachment. The eyebrows and lashes are well formed. Axillary and pubic hair is abundant and of normal distribution.

The cheekbones are prominent (American Indian type). The joints are large and pliable. The breasts are well developed.

The palatal arch is low and the dental ridge fairly wide. The teeth are irregularly placed. The upper central incisor teeth are markedly spaced and show transverse striations near the gums. The upper lateral incisors are absent (Fig. 5). The first upper premolars of the second dentition have been extracted. The lower central teeth are crowded and show longitudinal ridging. All of the teeth have a dirty yellow color which is most marked near the gumline.

The thyroid gland is moderately and uniformly enlarged—simple goiter.

The blood pressure is 105/55; the pulse, 74; the buccal temperature, 97.4 F. The heart is negative as to murmurs. There are

Figure 5   Photograph of the teeth of Case No. IV.

numerous coarse rales throughout the right upper chest. There is definite tympanites over the right upper chest.

The reflexes are all present, active and equal. The knee jerks are very active. There is no clonus, tremor or Rombergism.

Radiographic examinations. The heart and mediastinum are negative. There is considerable inflammatory reaction in the hilus regions associated with peripheral radiation. The condition is most marked in the right chest.

A radiogram of the lateral head shows almost complete osseous bridging of the sella turcica. The sphenoid sinus is quite large. The epiphyses of the wrist and hand bones are open.

Laboratory examinations Sputum examinations were repeatedly negative for the tubercle bacillus; the urine is negative for sugar, albumin, pus cells and casts.

Diagnosis. The following diagnoses are made: present ailment chronic bronchitis; general, goiter (simple), myasthenia and faulty nutrition.

REVIEW OF LITERATURE

A dental surgeon, R. C. Lucas, in 1888 published data concerning several patients in whom an upper lateral incisor tooth

was absent, or if present, deformed and very small (1). These patients had children with congenital deformities, in most cases harelip and cleft palate. The only man in the series had an only child, a daughter, who, like her father, had no upper lateral incisor tooth. This author, from his observations concluded that "the absence of a lateral upper incisor tooth resulting from an arrest of development is to be regarded as a malformation closely related to harelip and cleft palate, and is capable of transmitting each or both of these deformities to a succeeding generation."

In a second paper, which appeared in 1904, Lucas states "that some dental surgeons present" at the presentation of his first paper "declared that lack of eruption of certain teeth of the second set was a matter of common observation, and that no clinical importance need be attached to it." However, the author still contended that such defective dental development is a danger signal as to results that might follow in succeeding generations.

The work of Lucas, aside from creating an immediate school of opposition, made little impression upon the medical and dental world, for the subject appears not to have been considered again until twenty-nine years later, when Kaplan, 1917, without presenting evidence, associated deformity and absence of the upper lateral incisors with the internal secretion of the gonads.

Kaplan (2), apparently unaware of the papers by Lucas, deals with the subject of the incisor teeth as follows:

"If the middle upper incisors carry a message from the pituitary, the lateral upper incisors certainly do the same from the gonads. So that when the gonads are teratologically ab ova, definitely abnormal, one is sure to find some abnormality in the upper lateral incisors. The relationship, if any, is a crossed one, so that the right upper lateral incisors may point to the left testis or ovary, and vice versa."

"It is also to be noted that the greater the deviations from normal, the more definite the markings in the dental department, so much so that the lateral incisors, as a result of marked gonad defect, may not have erupted at all. Such a dental situation is rare indeed, so is also the clinical condition presented by the patient who has it."

"In the male, small and stumpy laterals bespeak sexual impotence on the physical basis."

The year following the appearance of Kaplan's paper, Timme, 1918 (3), in discussing "a new pluriglandular compensatory syndrome," refers to the dental apparatus as follows:

"The teeth are usually delayed in their appearance. They also show certain characteristics. The lateral incisors, especially in girls, are frequently underdeveloped. The canines, likewise, are either underdeveloped or else take on the flat appearance of incisors, losing their fan-like appearance."

An extensive search of the literature has been unproductive of further information save the incidental statement of Mebane (4). This author, in discussing "the teeth in childhood," states that "congenital absence of any permanent teeth may occur" and that "absence of one or both upper lateral incisors is the most common." Aside from this statement the subject is not discussed except to state that extraction of the tooth opposite the absent one is one of the few instances in which extraction is justified in the treatment of malocclusion.

<center>DISCUSSION</center>

Consideration of the subject of malformation or congenital absence of the upper lateral incisor teeth, as previously noted, has given rise to three distinct schools of thought. In brief, the contentions of the three schools are as follows: (1) Lucas believes the condition to be an indication of the appearance of transmissible developmental malformations; (2) Kaplan asserts that the anomaly is the result of a gonadal deficiency; and (3) Timme states that it is indicative of a pluriglandular compensatory syndrome. To these should be added a fourth school. This latter school, although not recorded in the literature, as far as I have been able to ascertain, while recognizing the facts, contends that such have no clinical significance aside from that of human curiosity conditioned by the presence of the unusual.

It would appear that factors other than those already mentioned should be thoroughly considered before there will be forthcoming a feasible theory to explain the causation and meaning of developmental anomalies of the upper lateral incisor teeth. The question of the influence of periapical abscesses of the deciduous teeth upon the buds of the permanent set, the question of the elimination of unnecessary bodily members by processes of evolution and influences of environment, and, also, the question

of the hereditary nature of transmission of congenital defects and developmental arrests must be considered as possible factors in the production of dental anomalies before the dictum of either Lucas, Kaplan or Timme can be accepted without reserve. Investigation along such lines, of necessity, are laborious; however, ease should not prejudice to the extent of permitting one to deny any significance of so definite a phenomenon as the congenital absence of a tooth, especially if such is found to be a transmissible character.

HEREDITY AND THE UPPER LATERAL INCISORS

If the contentions of Lucas are correct, then the problem of the congenital absence of the upper lateral incisor teeth is reduced to a consideration of teratogenic factors: a study of *progeny generally, and teratogeny specifically.*

It is not feasible at this time to deal extensively with the problems of heredity; however, the genealogies of the patients whose case histories have been presented are of sufficient interest to warrant comment.

The mother and two sisters of the first patient have very small, peg-like upper lateral and massive central incisor teeth. The deformity of the incisors is more pronounced in the three sisters than in the mother. According to tradition, the maternal grandmother had the normal number of teeth, the upper lateral incisors showing slight torsion but of usual size. In this instance it appears that the dental anomaly was transmitted through the female line and that it has become more marked in each successive generation. Because of this fact one wonders if succeeding generations will have members showing congenital absence of the present deformed teeth.

The genealogy of the second patient is of interest in that a congenital absence of the right upper lateral incisor has appeared in four successive generations. As shown in Fig. 2, transmission of the dental anomaly has occurred only through the female line. Another point of interest in this genealogy is that of the ten children (seven girls and three boys) born to the patient's mother, four girls and two boys, a total of six children, are minus an upper right lateral incisor, save one girl who is deficient in the left lateral incisor. Because of this latter fact the question is raised as to the probability of bilateral absence of

the upper lateral incisors in members of succeeding generations.

Special interest is attached to the family history of the third patient because of the array of dental anomalies. The maternal grandmother, who lacked the upper lateral incisors, gave birth to nine children, including twins of opposite sex. Of the five girls, three had a dental condition similar to that of the mother and one had an absence of the right upper lateral incisor. One of the boys had teeth like his mother. The boy twin died young; the other two boys had the normal number of teeth. The third child, a girl, who had congenital absence of the upper lateral incisors, gave birth to a girl and two boys. The girl had congenital absence of the left upper lateral incisor. She married and has two daughters, one of whom has a dental anomaly similar to that of her mother.

The point of interest here is the partial recovery from the dental anomaly in the third and fourth generation; a condition quite the opposite that of the first patient. One brother, the patient, had absence of the upper lateral incisor the same as his mother and maternal grandmother. He married a woman who came from a line of diabetics, and herself has diabetes mellitus. She became pregnant five times, but none of the children lived longer than a few days after birth. Because of this, nothing can be said concerning the possibility of transmission of the dental defect through the paternal line. However, an uncle of the patient, who had congenital absence of the upper lateral incisor, married and had three boys and three girls, all of whom have the normal number of teeth.

It is unfortunate that the pair of twins in this family did not live to maturity, inasmuch as the girl, who survived to adulthood, has congenital absence of a lateral incisor, as did her mother. Had the boy grown to maturity and possessed the normal number of teeth, we should then have had a condition somewhat analogous to that of mongolianism appearing in one of two-sexed twins. Such a condition would of necessity demand a close differentiation between hereditary and congenital factors in the production of such variations in twins.

The fourth patient, though showing marked deformities in the dental apparatus, is free from any known hereditary factor to account for her condition.

Congenital anomalies other than those shown in the dental

sphere have not occurred in the genealogies of the four patients presented. Further, in a series of 16 cases of congenital absence of upper lateral incisor teeth, the family histories of whom are available, there has not appeared a single known instance of harelip or cleft palate. The only instance of malformation was that shown by a maternal uncle who was born without arms. These observations are quite different from those collected by Lucas; however, the present genealogical findings in no way vitiate those of previous observers. The collected facts remain as observed; the theories evolved for explanation of the facts, of necessity, are based upon considerations of available data.

FERTILITY AND THE UPPER LATERAL INCISORS

The statement of Kaplan, "when the gonads are teratologically ab ova definitely abnormal, one is sure to find some abnormality in the upper lateral incisors," offers little solace. Moreover, the statement appears ambiguous in that one is permitted to assume either that the dental anomalies are conditioned by monstrosity of the ovum, that is, of the germ plasm, or by deficiency of the postulated internal secretion of tissues anatomically associated with germ cells. The use of the collective term gonad is always confusing in that one is forced to interpret its meaning, and such interpretations often give rise to much misunderstanding.

If Kaplan means that teratological conditions in the germ tissue are responsible for dental anomalies, then his explanation of the phenomenon is similar to that of Lucas, namely, the appearance of a transmissible anomaly. On the other hand, if he means that the appearance of dental anomalies is the result of the gonads, then one is forced to conclude that the anomaly is either the result of a congenital (accidental) defective endocrine principle or that the endocrine deficiency is the factor transmitted. Acceptance of the latter conclusion in no way simplifies the explanation of the conditions "teratologically ab ova" which cause the dental anomaly. In fact, such a conclusion merely shifts the transmissibility of dental anomalies from dental anomalies, as such, to that of an endocrine principle which, because of its presence, permits the dental anomaly to appear.

From the nature of Kaplan's statements I assume that he

is dealing with the relation of the internal secretions of the gonads to the upper lateral incisors. In any event, it appears that much evidence must be compiled before such a relationship can be accepted with safety. Moreover, there should be complete differentiation between reproductive (germ plasm) and bodily (somatoplasm) functions when speaking of the gonads.

The contention of Kaplan, also that of Timme, would seem vindicated in the light of the findings of my first patient. However, if this patient is to be classified as belonging to the pluriglandular syndromes, then not she alone but also her mother and maternal grandmother must be similarly classified, for each was small of stature—sixty-two inches—and each was subject to marked irregularity of menstruation. It appears, however, that the patient's maternal ancestry were far from being sexually impotent or unproductive; the grandmother gave birth to five boys and one girl, and the mother to three girls and a boy, and there were two miscarriages.

There is no evidence of sterility in the mothers of the second and third patients. For instance, the mother of the second patient, who lacked the right upper lateral incisor tooth, a condition similar to that of her mother, gave birth to ten children (seven girls and three boys), six of whom never developed a lateral incisor. The oldest child, a girl, with dentition like that of her mother, married and give birth to four girls and a boy. The oldest daughter, like her mother, grandmother and great-grandmother, is minus a right upper lateral incisor.

The grandmother of the third patient, whose dental anomaly consisted of absence of both upper lateral incisors, gave birth to nine children, including a pair of twins. Three of the girls and one boy had dental characteristics similar to those of the mother, and one girl was deficient the right upper lateral incisor. Eight of the nine have married, and seven have families; a total of twenty-four offspring.

The factors responsible for the establishment of sexual maturity appear to have been normal in the cases reported. Menstruation was established in the first patient at twelve years and three months; however, the menstrual periods have never been regular. In the second patient, maturity occurred at the age of fourteen years. In her case menstruation has continued regular save for a period of about six months following an acci-

dent. Menstruation, in the fourth patient, did not appear until the age of fifteen years. Sexual maturity occurred in the third patient at the age of thirteen years. Libido and potentia are considered normal or possibly slightly accentuated in the first patient. The third patient asserts that libido has been marked since the age of thirteen years and that venery has been excessive. Just the opposite condition was found to exist in another patient, a man, who has congenital absence of the right upper incisor tooth.

Conclusions relative to the fertility of persons possessing congenital anomalies of the upper lateral incisors must wait upon more extensive data than are now available.

INTERNAL SECRETIONS AND THE UPPER LATERAL INCISORS

I do not wish to discuss at length or intend to draw conclusions relative to the possible endocrine significance of anomalies of the upper lateral incisors. I do, however, wish to present the endocrine aspect of the four patients, the case histories of whom have been given.

The clinical findings of the first patient are such as to indicate a rather marked dyspituitarism. This assumption is derived from the fact that the torso length is less than that of the lower portion of the body and the span greater than the height. To these may be added the small, nearly bridged sella turcica, the small sinuses, the small hands and feet with tapering phalanges, the terminal digits which are free from tuberosities or tuftings, the broad pelvis and genu valgum. The slow pulse, low temperature and blood pressure, the high carbohydrate tolerance, the girdle, mons and mammary adiposity, intestinal atony, freedom from uterine cramps and periods of apathy, may also be taken as evidence of a functionally feeble pituitary gland.

According to the teachings of Falta (5), an osseous development as shown by the patient (the distance from the symphysis to the heel greater than from the symphysis to the top of the head) is diagnostic of primary genital dystrophy. However, sexual maturity (menstruation, libido, potentia and secondary sex characters) appeared early in this patient, and with their appearance growth ceased. In spite of the early appearance of sex maturity, there has continued a marked degree of amenorrhea and there is, at the present time, a definite growth

of hair on the upper lip. These gonadal symptoms, according to Engelbach (6), may be explained upon an assumption of post-adolescent hypoantuitarism.

Disturbed endocrine function is further evidenced by the depressed basal metabolic rate. This, together with the fact that thyroid medication resulted in a marked improvement of the general health, is indicative of an under-functioning thyroid gland. Certain other symptoms are readily explainable by assuming a weakened function of the suprarenal bodies, but of this, enough. In concluding this case we may diagnose as follows: (1) primary genital dystrophy; (2) postadolescent hypo-antuitarism associated with thyroidal and gonadal insufficiency; or (3) pluriglandular syndrome. Truly, in this patient Kaplan finds vindication for his gonadal theory of incisor anomalies; Timme of the pluriglandular theory, and Lucas for that part of his theory which contends for the transmissibility of such characters.

The general osseous development of the second patient is quite similar to that of the first. The leg length is 10.5 cm. greater than that of the torso, the span is 9 cm. greater than the height, and the hands are small and tapering. The sella turcica, however, is roomy, and the sinuses are of average size.

The increased carbohydrate tolerance, the typical moderate girdle, mons and mammary adiposity, epileptiform seizures, intestinal inactivity and absence of uterine cramps, may be looked upon as evidence of hypophyseal deficiency. In opposition to this assumption is the absence of apathy, a normal basal metabolic rate and the menstrual disturbances so frequently associated with anterior lobe disorders (Engelbach). However, the present type of adiposity rather definitely incriminates the pituitary organ as responsible for her present status and an early primary genital dystrophy for her osseous development.

The third patient must be considered as showing initial endocrine disturbances if we follow the dictum of Engelbach relative to birth weights, for he weighed 13½ pounds when delivered. Overweight was continued until the ninth year, at which time he "thinned out" and grew rapidly until the establishment of sexual maturity at the age of 13 years. This growth period may be looked upon, as suggested by Engelbach, as one of active function of the pituitary gland. Continuance of an active pitu-

itary function is evidenced by the large and separated upper incisors and a definite degree of spacing of the lower teeth. The peculiar bodily proportions (torso greater than lower length and span greater than height) and mild prognathism, also may be looked upon as pituitary characters.

Inhibition of growth (height) occurred in this patient, simultaneously with the appearance of sexual maturity. Sex instincts and functions, since their appearance, have been excessive. This condition may be looked upon as the result of either "hyperfunction" of the gonads primarily, or secondarily as the result of pituitary stimulation. In either instance the situation is quite opposite to that observed in the first two patients. Indeed, we may look upon this patient as giving evidence of very active gonadal and pituitary functions.

The acceptance of such a conclusion, of necessity, raises a difficulty in the acceptance of a theory of gonadal deficiency to explain the absence of the upper lateral incisor teeth unless one wishes to argue that gonadal functions, weak by nature, have been excited to excesses by reason of an unchecked pituitary gland.

The fourth patient, like the third, was overweight at birth and continued so until the attack of thrush during her second year. Growth was slow and menstruation did not appear until the fifteenth year. In spite of the family history, which is highly suggestive of pituitary dysfunction (an only sister with primary dystrophy adiposa genitalis, a very short mother, and a tall father), the patient's measurements are normal, i. e., the torso and lower measurements are equal. Aside from the information relative to the birth weight, measurements and date of onset of menstruation, but little is to be said relative to the endocrine system. The long continued series of infections have so occupied the clinical field that present conditions are not justifiably to be considered alone the result of endocrine factors. Indeed, it may be that the present dental anomalies are explainable on the basis of an infectious process.

Before leaving the subject of the gonads I wish to call attention to the dental apparatus observed in a case of pseudohermaphroditism. The patient, who was twenty years of age, consulted her family physician because of the non-appearance of menstruation and sex instincts. Examination revealed a penile

organ about two inches long, with a well developed glans and prepuce and an indenture indicating the meatus (Fig. 6). The urethra, however, opened directly beneath the penile organ. A second opening, the vaginal inlet, barely admitted a probe. The breasts were undeveloped and appeared like those of a male. The

Figure 6 Photograph of the external genitalia of a case of hermaphroditism.

voice was heavy, the features coarse, and there was a definite growth of hair on the chin and upper lip.

Because of chronic trouble of the appendix and a possible marriage the patient underwent an operation for appendictis and amputation of the penile organs. At operation the internal

b. On an ill-developed upper lateral incisor tooth as a forerunner of harelip or cleft palate. Brit. J. Child. Dis. (Lond.), 1904, 1, 483.

2. Kaplan, D. M.: An endocrine interpretation of the dental apparatus. This Journal, 1917, 1, 208-221.

3. Timme, W.: A new pluriglandular compensatory syndrome. This Journal, 1918, 2, 209-240.

4. Mebane, D. C.: The teeth in childhood. Collect. Papers Mayo Clinic & Mayo Foundation, 1923, 15, 881-890.

5. Falta, W.: The ductless glandular diseases. Transl. & ed. by M. K. Meyers, Phila., 1915, P. Blakiston's Son & Co., 692 pp., 4.

6. Engelbach, W.: Classification of disorders of the hypophysis. This Journal, 1920, 4, 347-365.

CASE OF PLURIGLANDULAR DYSCRASIA

FRED S. MODERN, M.D., and GRENDON F. REED, M.D.

From The Physiatric Institute and Dr. Mills' Hospital,
MORRISTOWN, N. J.

The case described below is interesting for several reasons. It first appeared as a case of obesity and achondroplasia. Only close examination of the history, of the physical findings, and finally the x-ray plates, made it necessary to rule out this condition and seek for another clinical diagnosis.

Krabbe lately drew attention to the fact that cases of precocious puberty frequently simulate achondroplasia. He introduced for these cases the name pseudo-achondroplasia. Precocious puberty was also a prominent but not sole feature of our case. Further examination indicated that a number of the endocrine glands were involved. As in most such cases, the symptoms were not those of mere hyper- or hypo-function, but in the same gland there seemed to be partial functions exaggerated, while others were attenuated, thus presenting a picture of real dyscrasia.

Case No. 1759. Miss H. S., Hebrew, age 18 years, school-girl.

Family history on the father's side was negative. On the mother's side all the family are stout. One of the patient's aunts developed mild diabetes in her twenties and on slightly restricted diet has been sugar-free for a number of years.

A cousin of the patient developed dyspneic attacks at the age of eight-months. Roentgen ray examination showed an enlarged thymus. On x-ray treatment (two or three sessions) the condition cleared entirely.

Past history. The patient was delivered at term by forceps, with slight trauma to the forehead, which cleared in a week.

Her weight at birth was 7 or 8 lbs. She was a fully developed and very stout baby and weighed 33 lbs. at the age of one year.

At the age of four she had very mild scarlet fever, with complete recovery in six weeks without complications or sequels. She had measles at the age of seven years, and chicken-pox at eleven, both very mild, without complications. Chorea (?) at the age of 8-9 years lasted for a few weeks.

She started to talk at the age of six months and was able to talk fluently at one year. At the age of 18 months she spoke like a child of four years. Teeth came at the normal time. She started to walk at the age of 17 months.

She was able to read at the age of 5 years. In school she was always one of the best pupils, mentally very bright. Myopia was discovered at the age of 6-7 years.

61

At the age of 8-9 her breasts began to develop and grew unusually large. Two years later she started to menstruate. The first period lasted for about a week, the next did not come for two months, and since then she has menstruated regularly every four weeks. The second menstruation lasted about two weeks, the subsequent ones about 6-7 days with moderate discharge and slight pain.

The axillary and pubic hair developed at the age of 11 years. At the same time the hair of her head became coarse and dry. Her growth at this time was very slow and stopped entirely at 13 years.

She first became obese at the age of 5 months. A second increase of obesity occurred at the age of 9 years, at the same time as her breasts developed.

She is mentally very active and a great reader. She refused, as a child, to play with other children, because "they were stupid." Now she does not make any friends. She talks much, is extremely moody and has a disagreeable disposition. She feels sometimes very old ("190 years").

Physical examination. The height is 146 cm.; plantar-symphseal measurement, 58 cm.; plantar-umbilical distance, 74 cm.; distantia spinarum, 28 cm.; distantia cristarum, 24 cm.; distantia trochanterica, 30 cm.; humerus, 31 cm.; forearm, 21½ cm.; femur, 30½ cm.; leg, 30½ cm. The skull measurements were lost, but the circumference is unusually large. The weight is 160 lbs. There are fat pads over the shoulders, the lower part of the abdomen, buttocks and thighs. There is comparatively little fat on the thorax and limbs. The skin is smooth and tense, not dry. The hair is very thick and coarse. Axillary and pubic hair is scanty. There is a slight mustache.

The mammae are about 35 cm., nearly free of fat; on palpation they seem to consist of lobulated adenomas. At places there is slight tenderness; a few adenomatous nodes can be distinctly separated from the surrounding tissues, varying in size from a walnut to an orange.

The pupils are equal, and react well to light and accommodation. The reflexes are normal. The thyroid is not palpable. A few lymph nodes in the axilla are palpable. The teeth are intact. The tonsils are somewhat enlarged. The lungs are normal. The heart is small; the sounds are well defined, and there are no murmurs. The pulse is regular; the rate at rest is 82, after exertion 98, and it returns within 1½ minutes to the former rate. In the abdomen there are no masses; slight tenderness is felt over MacBurney's point. No examination of the genital organs was made.

The red cell count was 5,500,000; leucocytes, 9800; polymorphonuclears, 61%; lymphocytes, 32%; eosinophiles, 4%; basophiles, ½%; monocytes, 2½%; hemoglobin (Tallquist), 90%. The blood sample was taken 3 hours after breakfast.

Eye examination gave the following results: O.D.9.200, —3.50 axis 30, 15/40 two letters; O.S. —1.25— —3.00 axis 150, 150/30 two letters. The muscle test shows an exophoria of 3° for distant vision and a left hyperphoria of 1°. The ophthalmoscopic examination shows negative fundus. The examination of her fields of vision by the perimeter shows the field for form to be approximately normal. In the right eye there is a cutting off above of about 15°. The field for blue is quite contracted in both eyes (more in the left), and the field for both red and green is contracted. Examination did not confirm any pressure from the pituitary gland or nasal sinuses upon the optic nerve. (Dr. Calvin Williams, New York.)

Basal metabolism tests were as follows: January 31,—20% (before thyroid treatment); February 23, +11% (5 grs. of thyroid twice

daily); March 29, —3% (thyroid stopped).   (Dr. Benjamin Jablons, New York.)

Laboratory findings.

Date	Proteins Grams.	C. H. Grams	Total Calories	100 C.C.	100 C.C.	100 C.C.		Urine S.G.	Urine NaCl 3m	Body Wgt. Lbs.	Remarks
May 9	Unweighed		Low	220			700	1020	515	....	Diet contained 2 gm. of salt. Thyroid 5 grains.
10	Unweighed		Low	104	614	26	450	1018	412	160	Thyroid 5 grains.
11	Unweighed		Low				400	1016	371	....	B. P. 136/84. Thyroid 5 grains.
12	Unweighed		Low	.			650	1026	041	159	Thyroid 5 grains.
13	Unweighed		Low				300	1024	049	. . .	Thyroid 5 grains.
14	Unweighed		Low				400	1026	058	156	Thyroid 5 grains.
15	Unweighed		Low				300	1026	062		Thyroid 5 grains.
16	Unweighed Discharged		Low					.	....	155	
June 3	.....	.....	.	150	552	32		.	....	158	Office report.

X-ray findings. Roentgenograms were taken of the skull, pelvis, knees, elbows and hands.   The skull plate shows the sella turcica to be of normal shape and size.   The processus clinoideus anterior is somewhat overhanging, the posterior wall of the sella slightly indistinct. No other abnormality is observed.   The pelvis is large and of typically female form.   The ossa ilei are broad.   The sacrum is short, broad, and triangular.   The head and neck of the femur are fused, as are the greater and lesser trochanters.   The lower epiphysis of the femur and the upper epiphysis of the tibia and fibula are ossified. The elbow presents the normal picture of an adult.   Ossification of the lower epiphysis of the humerus and the upper epiphysis of the radius and ulna is complete.   The radiogram of the hand shows closure of the lower epiphysis of the radius and ulna, and ossification of the carpal and metacarpal bones and of the phalanges.   The fourth *metacarpal of the right hand is shorter and broader than the third* and fifth metacarpal of the same hand, and the fourth metacarpal of the left hand.   This is a sign of constitutional inferiority.   ·

According to the above history and findings, we may summarize the following symptoms pointing to a disturbance in the endocrine system: premature development of the intellect; precocious development of secondary sexual characters; onset of menstruation with obesity; hyperglycemia; lowered basal metabolism; premature closure of epiphyseal lines; infantile skeletal proportions; and a low urinary output.

DISCUSSION

Szondi has recently described an endocrine complex and certain new groups of endocrine disturbances of pluriglandular origin.   He distinguishes between an endocrine asthenic and endocrine dysthenic type.   The asthenic type coincides with what

is commonly known as pluriglandular insufficiency, while the latter group comprises the endocrine dysfunctions.

The first group is characterized by absence of hyperfunction of any gland, while the second group comprises glands with decreased, normal and increased functions. The subjects with undergrowth have the gland formula: depressed function of the thyroid, hypophysis and adrenals, hyperfunction of the gonads, characterized by early closure of the epiphyseal lines, normal or supernormal circumference of the skull, hypergenitalism, obesity, vagotony, schyzothymia with, in case of mental retardation, severe deficiency. Patients with overgrowth have the opposite gland formula.

This schema covers nearly entirely the clinical details of our case. However, in the analysis it is frequently difficult to decide whether a particular symptom is due to one gland or to another.

Symptoms attributable to the *thyroid* are the lowered basal metabolism, the typical coarseness and dryness of the hair and low urinary output (?). Only the two first symptoms are unquestionably of thyroid origin. Rowe emphasized particularly that in border-line values of basal metabolism the technic should be watched carefully. This was done in our case, and the three subsequent readings are a fair indication of the effect of the treatment which was followed at that time by the patient. If the lowering of the basal metabolism were not due to the thyroid it should not have responded to thyroid medication· (Plaut). The hair was of the typical myxedematous type; it curiously developed coincidentally with the patient's menstruation. Puberty is the usual time of development of goiter in girls, whether as a compensatory factor of some kind is problematical. In our subject, however, puberty led to a further increase of thyroid deficiency.

The adiposity and the appearance of the skin suggest the involvement of the *hypophysis*.

Engelbach has given recently an excellent review of endocrine adiposity. We found his observations confirmed in our obesity cases due to endocrine disturbance. In this patient the fat distribution was characteristically of the girdle type. While the thorax and mammae were nearly fat free, the shoulders, arms, lower abdomen, buttocks and· thighs had enormous fat

pads. The hand was slender; there was no trace of a dorsal hand pad.

The skin resembled Lisser's description of the hypopituitary skin. To quote Lisser: "The skin in hypopituitarism presents interesting changes. It is quite unlike the hypothyroid or myxedematous. It may be somewhat thick, though often it is thin, but it is not rough or scaly. It is dry and smooth as a rule, sometimes like the skin of a baby or a child."

The other symptoms which might be due to the pituitary, such as growth disturbance and retarded water metabolism, will be discussed later.

The rôle of the suprarenals is questionable. It seems fairly well established by experimental and clinical experience that the suprarenal cortex is in intimate relation with the gonads and the secondary sexual characters. Jaffe and Marine have recently shown that in rabbits destruction of the suprarenal cortex is followed by an increase of the interstitial cells of the ovary by about 70%. An analagous influence upon the testis was missing. Adler, on the contrary, found that in tadpoles only the development of the male animals was promoted. Clinical observations corroborate the promoting influence of excessive suprarenal cortex activity upon genital development.

A review of precocious puberty recently published by Reuben and Manning enumerates 21 cases with tumors of the adrenals. Other cases of precocious puberty due to the adrenals are reported by Sézary, Hamilton, Meissner and others. In all these cases a tumor was found actually at operation or necropsy. In Meissner's case the diagnosis was founded upon finding a mass in the left hypochondrium situated dorsally.

We do not find any focal symptom of a suprarenal involvement. Moreover, in nearly every case of precocious puberty due to suprarenal function the secondary sexual characteristics were of male character (hirsutism). In our patient, except for a slight mustache, which we noticed also in her mother, and which is common in Jewesses, and a few hairs between umbilicus and mons veneris, nothing of this kind was observed. It is also pointed out that in pineal as well as in suprarenal involvement the breasts are well developed but small, while in our patient the unusual enlargement of the mammae was the most disturbing symptom. The mentality, except for pineal cases, is usually

retarded or adequate to the age. In this case it was premature. A suprarenal involvement seems, therefore, improbable.

The same holds for the pineal gland. Unless there are unmistakable focal symptoms or symptoms of increased intracranial pressure or x-ray or autopsy finding, the involvement of this gland should not be considered. Misinterpretations, however, may occur, as in the case of Oesterreich and Slawyk, in which, in a cranial roentgenogram, an unequal distribution of calcaria in the parietal bones was interpreted as calcareous deposits in the pineal. The autopsy showed that though there was really calcification in the epiphysis, it was located above and behind the place where it was supposed to be.

It is doubtless true that simple atrophy may occur in any organ for unknown reasons, and hence in the two last mentioned glands. But at present the physiology and pathology of these endocrine organs is so unsatisfactorily recognized that a reference to them should be made only if the clinical symptoms are perfectly uniform and strictly point to a localized lesion.

Whether a simple primary hyperfunction of the gonads can establish itself without any further hormonal and neural stimulus is not clear from the literature. We do not include cases in which the hyperfunction is due to a malignant degeneration of the ovaries or testis (case of Sacchi and of Knopfelmacher).

An interesting contribution to the metabolic function of the ovaries was lately published by Veil and Bohn. They found that the feeding of ovarian extract affects the salt and water metabolism in normal persons, as shown chiefly in the urinary output and body weight. The effect becomes marked especially after the cessation of the administration of the extract. In this afterperiod there is a powerful hyperchloruria and polyuria, then in the following days a secondary storage of salt. It seems that the omission of the ovarian extract causes a state of dehydration, while ovarian extract causes tissue hydration. A disturbance of the salt and water metabolism is fairly plain from the patient's records. The urinary output was always low, and on salt-free diet the urinary NaCl output fell very quickly to a very low level, as if the body would retain its salt reserves with great stubbornness. This picture seems to be close to that described by Bohn and Veil.

The clinical picture suggests also hyperactivity of the ovaries. Tierney lately reveiwed this subject, citing a number of cases of precocious puberty, and inserting a differential diagnostic table of precocious puberty due to pineal, adrenal and hypergonadism. Except for the precocious mental development all the other symptoms of our subject coincided with the signs of precocious puberty following hypergonadism. Precocious mental development is a sign of pineal involvement, but since no other symptom of an epiphyseal lesion was found, all we can say is that hypergonadism can be associated with premature mental development. Cases of precocious mental development and adrenal involvement have been reported (Herzog).

The hyperglycemia seems to be of the obese type and hereditary in the family. Whether it is in any relation to the insufficiency of other glands than of the pancreas is doubtful, since Allen in particular has shown that the adrenals and the thyroid have no direct effect upon the pancreas. The hyperglycemia was easily abolished by dietary restriction.

For the complex symptoms, such as the shortness of the long bones, the premature closure of the epiphyseal lines, and the low urinary output, it is the thyroid, the hypophysis and the gonads which must be considered.

Engelbach and MacMahon have lately reviewed the osseous development in endocrine disorders. They give the age of 18 to 20 years for the union of the lower epiphysis of the ulna, lower epiphysis of femur, upper epiphysis of tibia and the upper and lower epiphysis of fibula. Except for the lower epiphysis of the fibula, for which no plate was secured, all the other above mentioned bones were found to be closed. According to the patient's history, her growth became slow at the age of 11 years and ceased entirely at 13 years. It seems, therefore, probable that the fusion of the bones occurred some time ago, possibly at her 13th year, when she stopped growing.

A juvenile hyperactivity of the anterior lobe of the pituitary gland causes gigantism, in adult age acromegaly. Shortness of the long bones is due to underfunction of the hypophysis.

While the hypophysis controls the length of the bones, the thyroid and gonads control the termination of growth. In myxedema the chondral lines remain open for an abnormally

long time. In eunuchs the growth is promoted by late fusion of the bones.

The infantile skeletal proportions which we found in our patient are rather a sign of general growth disturbance than of a particular deficiency. The undergrowth in our subject is apparently due to an anterior lobe deficiency, the early chondral fusion to the hyperactivity of the ovaries.

The water metabolism is governed hormonically by the thyroid and the gonads. Eppinger has shown in particular that the administration of thyroid extract is followed by a profuse diuresis in certain cases of edema. The myxedema is due, according to this conception, to an altered colloidal state of the tissues.

The insufficiency of the posterior lobe, or according to other views, of the infundibular region of the tuber cinereum, causes diabetes insipidus. However, it is doubtful that diabetes insipidus represents a real disturbance of the water metabolism. More and more evidence is furnished that it is due to inability of the kidney to produce a concentrated urine, which is made possible under normal conditions by an extrarenal factor so far unknown.

If we consider the work of Bohn and Veil, and on the other hand the fact that the urinary output did not increase on thyroid medication, it seems probable that the gonads are involved in this disturbance.

Therapy. The patient was treated prior to her admission to the Institute with various gland preparations for a long period of time. Thyroid had a distinct effect in that her basal metabolism became normal. The administration of pituitary and ovarian extract, even over a long period of time, had no effect.

The therapy in the Institute consisted of a low calory diet, which reduced her blood sugar to normal, and five grains of thyroid daily, which resulted in a prompt loss of weight within a week. On returning home she abandoned the diet and relapsed.

<div align="center">SUMMARY</div>

1. A case of precocious puberty with hyperglycemia is described.

2. The precocious puberty is apparently due to hyperactivity of the ovaries. There are symptoms of a bilobar pituitary, thyroid and pancreatic deficiency.

3.   Hypergonadism and precocious mental development can exist together.

BIBLIOGRAPHY

Adler: A function of the adrenal cortex. München. med Wchnschr., 1922, 69, 797; also, Klin. Wchnschr. (Berl.), 1922, 1, 181.

Allen: Experimental studies in diabetes. The internal pancreatic function in relation to body mass and metabolism. The influence of the thyroid upon diabetes. J. Metab. Res. (Morristown), 1922, 1, 619. The relation of the adrenals to diabetes. Ibid., 1923, 3, 589.

Engelbach: Endocrine adiposity. Med. Clin. N. Am. (Phila.), 1922, 6, 1.

Engelbach & MacMahon: Osseous development in endocrine diseases. This Journal, 1924, 8, 1.

Hamilton: Glimpses into endocrinology. Canad. M. Ass. J. (Toronto), 1922, 12, 209.

Herzog: Ein Fall von allgemeiner Behaarung mit heterologer Pubertas praecox bei dreijährigen Mädchen. München. med. Wchnschr., 1915, 62, 6.

Jaffe & Marine: Influence of suprarenal cortex on gonads of rabbits, etc. J. Exper. M. (Balt.), 1923, 38, 107.

Knopfelmacher: Demonstrationen. Wien. klin. Wchnschr., 1903, 1906.

Krabbe: L'achondroplasie et les cas pseudo-achondroplasiques. Rev. neurol. (Par.), 1923, 30, 127.

Lisser: Hypopituitarism and its treatment. This Journal, 1922, 6, 16.

Meissner: Endocrine Störungen im jugendlichen. Alter. Med. Klin., 1922, 18, 1306.

Neurath: Die vorzeitige Geschlechtsentwicklung. Ergebn. d. inn. Med., u. Kinderh. (Berl.), 1909, 4, 41.

Oesterreich & Slawyk: Riesenwuchs und Zierbeldrüsengeschwulst. Virchow's Arch. f. path. Anat. [etc.], (Berl.), 1899, 97. 475.

Plaut: Gaswechseluntersuchungen bei Fettsucht und Hypophysiserkrankungen. Deutsches Arch. f. klin. Med. (Leipz.), 1922, 139, 285.

Reuben & Manning: Precocious puberty. Arch. Pediat., 1922, 39, 789; ibid., 1923, 40, 27.

Rowe: The diagnosis and treatment of thyroid diseases as controlled by the metabolic rate. This Journal, 1923, 7, 256.

Sacchi: Di un caso di gigantismo infantile con tomore di testicolo. Riv. sper. di freniat. (Reggio-Emilia), 1895, 21, 149.

Sézary: Les symptoms endocrinnien commons. Presse méd. (Par.), 1922, 30, 1075.

Szondi: Schwachsinn und innere Sekretion. Abhandl. a. d. Grenzgeb. d. inn. Sekr. (Budapest), 1922, 1.

Tierney: Precocious puberty. Med. Clin. N. Am. (Phila.), 1922, 6, 31.

Veil & Bohn: Beobachtungen des Wasser und Salzwechsels bei Thyreoidin und Ovarialextractbehandlung. Deutsches Arch. f. klin. Med. (Leipz.), 1922, 139, 212.

AN ENLARGED THYMUS IN AN INFANT; TETANY AFTER X-RAY TREATMENT

M. J. KONIKOW, M.D.

BOSTON, MASS.

The following case is reported because of its endocrine interest.

Baby M., male, was the fourth child born to Mrs. M., on June 26, 1922. Its weight at birth was eight pounds. There was nothing abnormal in the prenatal history of the mother, nor was the birth of the child accompanied with any difficulties. It was in all respects a normal delivery. The only abnormality about the baby was his breathing. With his first breath he developed an inspiratory crowing, which was.loud enough to be heard quite a distance away. His very labored breathing was one of extreme dyspnea. At times he would even become cyanotic. The dyspnea and cyanosis would occasionally subside, or somewhat diminish, but the crowing would always persist, even during his sleep. Outside of this, no other abnormalities were found.

On July 8, 1923, Dr. S. Robins took an x-ray plate of his neck and chest and the following report was submitted to me: "There is a large, dense shadow overlapping and merging with the shadow of the base of the heart. These findings are consistent with a large thymus."

This was confirmed by another x-ray examination on July 18, 1922, at the Massachusetts General Hospital, of which I quote the following report: "Plates of the chest show markedly increased supracardiac area of dullness very suggestive of enlarged thymus."

It was clear, therefore, that the symptoms present in this baby were due to an enlarged thymus, pressing upon the trachea.

It was deemed best to treat the enlarged thymus by x-ray. Two treatments were given: one on July 17, 1922, the other about a week later. A noticeable improvement of the breathing followed these treatments. The dyspnea and cyanosis would come only when crying, while during the quiet intervals the child would breathe fairly well. This improvement continued until July 31, 1922, when the first attack of typical tetany appeared, which did not leave the patient until his death from pneumonia on March 3, 1923.

There was hardly a day when the baby would not be attacked by tetany, two or more times. The x-ray treatments were stopped for reasons to be explained later, and other therapeutic measures instituted without, however, any relief. Among drugs used were bromides, small doses of luminal, also calcium lactate in 5 gr. doses, plain, or in combination with parathyroid gland in doses of gr. 1/40 to gr. 1/20 several times a day.

In spite of being a breast baby, its gain was very slow, its weight at the time of death being about thirteen pounds, representing a net gain of about five pounds in a little over eight months.

The family history is perhaps interesting in that on the mother's side one of the parents (father) died of tuberculosis, and on the father's side a brother died of cancer. The baby's mother was an apparently healthy woman of thirty-two, with nothing abnormal in her history. Except for the first child, who had to be delivered instrumentally after three days of labor, and who died twenty-four

hours after delivery, the other two children were born normally and continued to be normal. It is perhaps of interest that on February 23, 1924, she was delivered of a baby girl with club feet, and during the latter months of this last pregnancy she developed diabetes, which promptly subsided, however, after delivery.

DISCUSSION

The important findings in this case are as follows: 1. The extreme dyspnea accompanied by crowing inspiration with the very first breath of the child, 2. An enlarged thymus, as shown by x-ray examination on two different occasions; 3. The appear-

ance of tetany in the sixth week of the baby's life, after the enlarged thymus was subjected twice to x-ray treatments; 4. The failure to relieve the tetanic attacks either by calcium lactate, or by the desiccated parathyroid substance, administered separately or combined; 5. The possible relation of thymic enlarge-

ment in this case to the malformation of the feet (club feet) in a sister born about twenty months later.

That not all enlarged thymi are apt to cause disturbance in respiration or other symptoms was shown conclusively by Liss (1), who found an enlarged thymus without any symptoms in 42 per cent of the children roentgenologically examined. Greenthal (2) also found the thymus enlarged in ninety cases, out of which eighty-seven gave no history, nor presented any symptoms of thymic involvement.

From this it would be reasonable to conclude that it is not the size of the thymus that determines the symptoms, but its relation to the trachea in the thorax, and especially in the narrow superior opening of the thorax, the so-called "critical space of Gravitz." A superficially wide thymus may give an enlarged x-ray shadow, but is not deep enough to cause pressure upon the trachea and thus produce dyspnea. On the other hand, narrow but deep thymi may show a small x-ray shadow and yet be capable of producing most severe symptoms.

Pfahler (3) arrived at a similar conclusion. After diagnosing and treating by means of x-rays a large number of enlarged thymi, he expresses himself thus: " . . . We did learn, however, that the thymus can be enlarged without producing symptoms. This is not an argument that it is a normal or harmless condition, any more than enlarged tonsils in a child are a normal or harmless condition. On the other hand, thymic symptoms may develop, we believe, even when no enlargement is shown by the x-ray. For the x-ray can only show lateral enlargement and yet it is the anterior-posterior pressure which causes the symptoms."

In this connection it is interesting to note that Smith (4) produced experimentally simulation of enlarged thymi in eight guinea pigs by injecting paraffin into the thorax in the thymic region. None of these guinea pigs suffered from any effect of the pressure by the paraffin tumor in spite of its large size, as determined by autopsy three weeks later. Of course, this experiment was no proof that a really enlarged thymus was not capable of compressing the trachea and thus producing all the dyspnea symptoms. We must not forget that the paraffin, when injected into the thorax is in a liquid condition, and before it forms a solid mass it is therefore yielding to the normal structure of the

trachea, without compressing it. This would explain the absence of symptoms in Smith's experiments.

Now a few words as to the symptoms of tetany in our case. Was it due to the presence of an undoubtedly large thymus, or rather, as the writer thinks, to the subsequent x-ray treatments with a possible injury to the parathyroid glands? If the thymus would be responsible for tetany, why was the latter absent during the first five weeks of the infant's life, appearing only after two x-ray treatments?

I am aware of the fact that many authors consider the thymus responsible for producing tetany. Bash, as quoted by Hoskins (5), says: "Thymus plays an important rôle in the etiology of tetany." But Uhlenhuth (6) with his feeding experiments with thymus on salamander larvae (which have not parathyroids) and on the metamorphosed salamanders (which acquire parathyroids) has given, in our opinion, undeniable proof that the tetany produced in the former by thymus feeding was due to the lack of parathyroids, the internal secretion of which in some way neutralizes the toxic elements in the blood; and, vice versa, that the lack of tetany in the metamorphosed salamanders was due to the protective influences of the existing parathyroids.

It follows, therefore, that, even assuming the existence of a specific tetany toxin in the thymus, this toxin is apparently neutralized in the presence of effective parathyroids.

On the other hand, Collip and Backus (7), Grant and Goldman (8) and Barker and Sprunt (9) have shown that prolonged hyperpnea affects the carbon dioxide combining power of the plasma, thus disturbing the acid-base equilibrium of the blood, which condition, in their opinion, provokes tetany.

It would be difficult to explain the appearance of tetany in our subject as due to hyperpnea. Were it so, the tetany should have appeared much earlier in the infant's life.

It is, therefore, reasonable to assume that the x-ray treatments, while shrinking somewhat the enlarged thymus, shrunk or destroyed at the same time the sensitive apparatus of the parathyroid glands, which inevitably led to tetany. In support of this theory we will quote Grier (10), who, in discussing the preference of radium treatment in enlarged thymus, states: " . . . The difficulties in administering treatment to a small

baby are also considerable. The baby must be held by other persons who run the risk of exposure to high voltage currents and to the roentgen ray beam in their efforts to keep the patient still and in the proper position. Lead masks placed to expose the thymus area are apt to slip, and thus cause the treatment to be administered where it will do no good.'' If we substitute the last phrase, ''do no good,'' by the phrase ''do positive harm,'' it would fit our case much better.

The failure to relieve the tetanic attacks either by calcium lactate or by desiccated parathyroid gland, singly or combined, may lie in the faulty material manufactured; it may also lie in the destruction of the parathyroid hormone on its way to the blood system, via the gastro-intestinal canal, similarly to insulin, which is claimed to be ineffective when administered orally; it may finally be due to many other causes which we do not know about as yet.

The failure of calcium lactate to influence the frequency of the tetanic attacks is interesting in view of the accepted diminished calcium content of the blood in tetany patients.

As to the relation of thymic enlargements to other malformation, Greenthal (2) concludes that ''patients with congenital effects and malformations are more apt to have thymic enlargement than are other patients.'' While in this case the baby did not have any other malformations except the enlarged thymus, it may, nevertheless, be of some significance that his youngest sister was born twenty months later with well developed club feet, an abnormal position of the feet which is ordinarily assumed by a child during a tetany attack.

To what extent this abnormality may have been a mere coincidence it is hard to say; but it may be more than coincidence that the unknown prenatal condition of the mother expressed itself in one case in an enlarged thymus, in the other, in club feet.

SUMMARY

The case is reported of an infant born with an enlarged thymus, with all the symptoms of severe dyspnea present with his first breath and with tetany following about five weeks later, after two x-ray treatments were given.

Injury to the parathyroid glands by x-ray is advanced as an etiological factor of tetany in this case.

The failure of calcium and parathyroid treatment is noted. Also the relation of enlarged thymus to other malformations in children is noted and discussed.

BIBLIOGRAPHY

1. Liss, J. E.: Am J Dis Child (Chicago), 1922, **24**, 192.
2. Greenthal· Ibid., 433
3. Pfahler, G E   Arch. Pediat , 1924, **41**, 39
4. Smith, L. H.   Northwest Med (Seattle), 1923, **22**, 398.
5. Hoskins, R. G.   Endocrinology & Metabolism.   D. Appleton & Co., N. Y., 1922, **2**, 374
6. Uhlenhuth, E   Proc. Nat Acad Sc (Balt), 1917, **3**, 517, as reviewed in This Journal, 1918, **2**, 524.
7. Collip & Backus   Am J. Physiol (Balt.), 1920, **51**, 568.
8. Grant & Goldman   Ibid , **52**, 209
9. Barker & Sprunt   This Journal, 1922, **6**, 1.
10. Grior, G. W   Am J. Roentgenol. (N. Y), 1924, **11**, 141.

Book Reviews

Studio Delle Sindromi Ipertiroidee Nell' Eta Infantile.
Maria Ines Fini, Verlag L. Capelli, Bologna, 1924. Pp. 269.
Reviewed in Monatschr. f. Kinderh., 1924, 29, 191.

Outline of Endocrinology. W. M. Crofton. William Wood &
Co., N. Y., 1924. Pp. 126.

In small compass the author of this volume has condensed
much of the history, anatomy, histology, physiology, pathology
and therapeutics of the glands of internal secretion. It is a
book that general practitioners, or even laymen, can easily read
and comprehend. Unfortunately the outline is one that should
be read only by those of considerable discriminative ability, and
to such readers it will have little that is new or suggestive to
offer. Such statements as "in chronic infections the whole tone
of the tissues can be restored by giving spleen extract" and that
thymus "should always be used in rickets" are possibly true in
the author's experience but have scarcely been widely demon-
strated. Although thirty-one pages are devoted to the pancreas,
the term "insulin" is used but once and summarily dismissed
with the statement that "there are several products which have
been on the market for years that will serve equally well." Like-
wise the author departs from orthodoxy when he states that
"amylopsin, pancreatic amylase, converts cane sugar into
maltose." Such excerpts suffice to show the need of reading the
volume with careful discrimination.—R. J. Seymour.

A Diabetic Manual for the Mutual Use of Doctor and
Patient. Elliott P. Joslin, 1924. Lea & Febiger, Phila. &
N. Y., 3 ed., Pp. 211.

Little more than an announcement of a third edition of
Joslin's well-known manual is needed for readers of this Journal.
The new edition continues the general plan of its predecessor
but incorporates, of course, the newer work on insulin. It is
written in an entertaining way, and, although it contains much
technical information, is largely comprehensible to the non-tech-
nical reader. To the busy practitioner who desires as expedi-
tiously as possible to be put in touch with the best current theory
and practice in the treatment of diabetes the book should be a
godsend. It should be in every health library and might well
be kept on the doctor's waiting room table.—R. G. H.

AN INTRODUCTION TO THE STUDY OF SECRETION. Swale Vincent, 1924. Edward Arnold & Co., Lond. Pp. 168.

The author has brought together the chief data on a series of topics not previously all discussed in a single volume. As he states, one of the main objects was to examine the principal facts of secretion and internal secretion to see how far they may legitimately be included in a common category and thus to afford a bird's eye view of what is known of secretion as a physiological process. After a brief historical introduction, four chapters are devoted respectively to "Anatomy and histology of glands," "The physical and chemical mechanisms of secretion," certain "Special forms of secretion" and the secretions of urine, milk, skin and tears.

The last sixty-five pages of the book are devoted to the internal secretions, taking up systematically the histological and then the experimental and chemical evidences for the endocrine function of each organ. The illustrations, of which there are thirty-five, are judiciously selected and several are notably excellent. The book is written in the author's well-known lucid style and can be heartily recommended as a sound and satisfying treatise.

—R. G. H.

GOITRE: A CONTRIBUTION TO THE STUDY OF THE PATHOLOGY AND TREATMENT OF THE DISEASES OF THE THYROID GLAND. F. de Quervain; trans. by J. Snowman. 1924. William Wood & Co., N. Y. Pp. 247.

The general scope of the work can well be summarized in the author's own words. He aims "to describe those few methods which daily experience of the operation has impelled us to adopt, and to emphasize those details which are essential for a beginner to realize. We have no desire to teach surgeons who are satisfied with their own method; our remarks are only intended for those who are searching for a method, or are dissatisfied with procedures they have hitherto adopted." The book is written from Berne, Switzerland, where the author has had the advantages both of abundance of material and close touch with the methods and traditions of the well-known Swiss school.

The first seven chapters are devoted to such topics as anatomy, physiology, etiology, and so forth. The chapter on physiology is brief, and rather generalized and colorless. The author leans somewhat to the belief in a multiplicity of thyroid hormones. Two pages on the causes of goiter serve to record the author's belief that these may be numerous but that absorption of toxins from the intestines is probably the most important factor. Heredity, however, and iodin consumption are also regarded as important. An excellent objective description with

a classification of goiters is given.   The attempt to correlate
histological with functional deviations is specifically given up as
impracticable in the present state of our knowledge of the latter.
The problems involved, the author believes, are much more com-
plicated than is assumed by the Mayo school.   It is stated that
the margin of safety as regards the thyroid is very wide.   Much
less than the traditional one-fourth of the gland substance is
able to sustain normal function, and likewise the body is able
to deal safely with much more than the normal amount of
thyroid secretion.   As a method of assaying thyroid material
Stereuli's rat asphyxia test is given high rating.   Its simplicity
and sensitiveness would seem to commend it.   The method is
described on page 50.   The chapter on diagnosis is detailed and
well illustrated.   The Goetsch test is regarded as yet uncertain
and the Kottmann reaction as distinctly promising.

The latter half of the book is given over to operative treat-
ment of goiter.   Methods growing out of the author's wide expe-
rience are lucidly set forth.   The book ends with a good working
bibliography of nearly 30 pages.—R. G. H.

Abstract Department

The electrolyte shift in blood and tissues through adrenin action
(Die durch Adrenalin bedingte Elektrolytverschiebung in Blut und
Gewebe). Dresel (K.) & Wollheim (E.), Arch. f. d. ges. Physiol.
(Berl.), 1924, **205**, 375-380.

Simultaneous determinations of potassium and calcium in the
blood, tissues and nutrient solution containing surviving guinea-pig
intestinal strips show that adrenin injections cause an electrolyte
shift in the sense that calcium, and in most cases potassium also,
passes into the tissues.—A. T. C.

Epinephrin in the treatment of herpes zoster. Duke (W. W.),
J. Am. M. Ass. (Chicago), 1924, **83**, 1919.

Duke has had 4 years' experience with epinephrin in the treat-
ment of herpes zoster. He has been disappointed in its effect on the
vesicular lesions, but in more than half the cases it relieved the pain
almost immediately, if given in adequate dosage. In using
epinephrin in this condition, it is necessary to adjust the dose to
suit the individual case. The dose should be pushed until the
patient experiences relief or an epinephrin tremor. The amount
necessary to give relief or tremor varies in different individuals from
1 minim up to several cubic centimeters—in fact, it varies in the same
individual at different times almost to this extent. As a general
rule, it should be given subcutaneously in doses of about 0.5 cc. at
five-minute intervals, until the patient is either relieved or shows a
distinct tremor. When the tremor appears, the pain in the majority
of cases disappears. It usually returns in from 2 to 24 hours. The
dose of epinephrin can then be repeated and continued indefinitely
without injury to the patient. As a rule, it makes the use of mor-
phin unnecessary, or at least reduces its necessity to an occasional
dose.—Courtesy A. M. A.

The effect of adrenalin on the duration of the latent, the contraction
and the relaxation periods of skeletal muscle at rest and under-
going fatigue. Gruber (C. M.), J. Pharmacol. & Exper. Therap.
(Balt.), 1924, **23**, 335-351.

A marked decrease in the duration of the latent and contrac-
tion periods with an increased height of muscular contraction in
early contraction is produced by adrenalin chloride. The relaxation
period is lengthened in early contraction as well as when fatigue is
coming on. The effects upon perfused, isolated non-fatigued frog's
and cat's skeletal muscle are variable.—G. E. B.

Reactions of partially asphyxiated intestine to oxygen and to epinephrin. Hoskins (R. G.), & Hunter (E. S.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 143.

Intestinal segments of young adult rats suspended in Ringer's solution remained inactive until oxygen was periodically bubbled through the bath. The reactions thus initiated gradually increased and then decreased almost to zero. When adrenalin was introduced at an optimal concentration the reaction to oxygen and more especially the persisting tonus level was augmented.—G. E. B.

Experimental study of adrenal function (Experimentelle Untersuchungen über die Funktion der Nebennieren). Kisch (B.), Klin. Wchnschr. (Berl.), 1924, **3**, 1661-1663.

The adrenals were removed from rabbits by two stage operations at intervals of several weeks. The animals often survived for long periods in apparently good health. Autopsy of such animals showed neither adrenal rests nor accessory adrenals. In this connection Kisch cites Strauss' human case (1915) in which the subject enjoyed good health up to the age of 24 despite congenital total adrenal aplasia. The normality of doubly epinephrectomized rabbits is only apparent since, upon exertion, they are liable to sudden death (earlier observations confirmed by Kisch). Fettering these rabbits led to a fall in the blood sugar level rather than the characteristic rise. The weights of the adrenals of normal rabbits varied within wide limits; those of females were heavier than those of males; in more than two-thirds of the animals the left was heavier than the right (average weights, 286 and 247 mg., respectively). In most cases the gland remaining behind after unilateral adrenal extirpation was found at autopsy to be larger than probable normal. The blood sugar immediately after the operation was elevated, but after 5 hours fell below normal and after 40 hours gradually was restored. The animals gave a hyperglycemic reaction to hemorrhage, fettering or sensory stimulation, but this was less than normal in degree and was at times substituted by a hypoglycemic reaction. No significant effect of the operation on the lactacidogen or inorganic phosphorus content of the muscles could be detected, hence the weakness of adrenal deficiency is not to be explained by failure of metabolism intervening at this point. The liver was not lacking in glycogen after the bilateral operation. In two or three instances blood calcium was depressed immediately after the operation but elevated above normal later.—R. G. H.

Influence of suprarenalectomy in rabbits on antitoxin (diphtheria) formation. Marine (D.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 497-499.

With one exception the 5 animals lacking adrenals formed antitoxin as rapidly as or more rapidly than the controls, the Schick test being used as a criterion.—J. C. D.

Notes on suprarenal and pancreatic grafting. Pybus (F. C.), Lancet (Lond.), 1924, ii, 550-551.

Pybus reports two cases of Addison's disease, in one of which adrenal grafting was practiced with apparent success. A year after the illness began the patient had marked asthenia and bronzing and blood count of 2,200,000, but systolic blood pressure of 110. The adrenals were taken from a man who had just died of trauma. These were split and inserted subcutaneously in the patient. Ten days later the patient was able to walk 5 miles; six months later the pigmentation had disappeared. Two years later he had been for several months doing full work in a mine, after which pigmentation and weakness returned. Half of another human adrenal was then ingrafted, following which, for the past 4 years, the patient has earned his living as a hawker. At present he is slightly pigmented and has a blood pressure of 130-175 mm. In a second case nothing beyond a slight improvement in blood pressure was effected by adrenal grafting. In case of the pancreatic grafts the results were liquefaction and sloughing as would be expected, considering the rich enzyme content of the grafts.—R. G. H.

Organotherapy in Addison's disease. Rowntree (L. G.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 135-136.

Nine subjects were given desiccated whole gland and epinephrin to the limit of tolerance. Each patient experienced subjective improvement. The pigmentation decreased in all. Prolonged improvement was accompanied by increase in weight, decrease in the gastro-intestinal symptoms, and slight increase in blood pressure. Improvement began within one week after initiating treatment. Individual tolerance varied markedly. Intolerance was encountered in some cases.—G. E. B.

Vessel-reactions and adrenin-formation of the isolated adrenals (Gefässreaktionen und Adrenalinbildung der isolierten Nebenniere). Takenaga (K.), Arch. f. d. ges. Physiol. (Berl.), 1924, **205**, 284-292.

The vessels of artificially perfused dog adrenals frequently do not react, but often show marked contraction with adrenin. Histamine and choline cause contraction Perfusion of the isolated adrenals with Tyrode's solution shows in the perfused liquid an adrenin concentration up to 0.1%. The activity of the fluid does not markedly diminish with the duration of perfusion, which seems to indicate actual formation of adrenin during the perfusion.—A. T. C.

The share of adrenin secretion in the reaction to sugar puncture (Ueber den Anteil der Adrenalinsekretion an der Zuckerstich-wirkung). Trendelenburg (P.), Arch. f. d. ges. Physiol. (Berl.), 1923, **201**, 39-55.

Injection into rabbits of adrenalin in amounts less than 0.05 thousandths of a milligram per kilo per minute for one hour did not affect the blood sugar height. Amounts of 0.06 to 0.1 increased the blood sugar without producing glycosuria. Amounts between 0.1 and 0.3 gave a blood sugar value at the end of the first hour averaging 0.2%, with in many cases, glycosuria. Amounts above 0.3 almost always gave glycosuria. The adrenin content of the adrenals after puncture makes it probable that the adrenin output is responsible for the increase in blood sugar after puncture. In two experiments after puncture the adrenin output from the glands was above 0.5 thousandths milligram per kilo per minute, which is high enough to produce glycosuria within a short interval.—A. T. C.

Fundamentals of organotherapy. Asher (L.), Klin. Wchnschr. (Berl.), 1924, **3**, 1705-1708.

Asher discusses the difficulties of a scientific foundation for organotherapy. The conceptions of hypofunction and hyperfunction are—even in the best studied instances (thyroid)—to a large degree artificial constructions. In other cases—excessive production of epinephrin or of pancreatic secretion—such assumptions are so far merely speculations. It is different, whether the action of a hormone increases in a simple proportion to the amount injected or in a curve which reduces the interval between the threshold and the maximum of action. The matter is further complicated by the possibility of a change into the opposite action after this maximum is reached—for instance, the stimulating effect of small doses of thyroid preparations or of epinephrin on the automatic movements of the intestine and bladder, and the inhibiting action of large amounts. The point of this reversal depends on the condition of the tissue—not merely on the dosage. Asher produced with Mauerhofer experimentally in rats the extreme muscular weakness which is characteristic of Addison's disease. Yet organotherapy fails completely in this disease. He believes that the mechanism may be analogous to that demonstrated by Carlson and Luckhardt in parathyroidectomized animals. The endocrine function of the pituitary gland is doubtful, except perhaps in phenomena connected with acromegaly and gigantism. This does not, however, detract from the therapeutic value of its preparations in obstetrical cases and in diabetes insipidus.—J. Am. M. Ass., **83**, 1380.

Glandular therapy. Billings (F.), J. Am. M. Ass. (Chicago), 1924, **83**, 1000-1001.

Billings states that at the present time substitutional organotherapy alone seems to be based on substantial grounds, and this principle is of practical value only to a limited degree. The use of thyroid gland or of thyroxin in proper doses will overcome the results, partially or wholly, of deficiencies of the thyroid gland secre-

tion. Insulin used daily and properly will restore and maintain carbohydrate metabolism in conditions due to deficiency of the internal secretion of the pancreas. But substitutional organotherapy in morbid conditions of man or animals due to deficient secretion of the glands of internal secretion, by the oral administration of the fresh gland tissues or of dried or otherwise prepared glands, is in an unsatisfactory status. This is due in part to the fact that the active principles of the secretions of all the glands of internal secretion, with the exception of the thyroid, are apparently destroyed by the digestive juices of the stomach and bowel. Pituitary extract and epinephrin must be considered as pharmacodynamic preparations, because, up to the present time, the various preparations of pituitary and epinephrin do not appear fully to take the place of the glands themselves. It must be said, however, that pituitary extract appears to substitute for the gland for temporary periods. With the exception of thyroxin and insulin, the use of preparations of other glands of internal secretion, hypodermically or intravenously, has not afforded uniform and consistent results that can be definitely ascribed to the specific efforts of the internal secretions of the glands. However, it must be stated that the possible good effects of the administration of preparations of the glands of internal secretion subcutaneously or intravenously may be masked by the reactions of the body to a foreign protein administered in the same manner. Substitutional organotherapy by the transplantation of fresh gland substance has been successfully accomplished, but the length of time during which engrafted tissue retains its specific character and function is variable and uncertain, and the results have been of short duration and of limited value. The present furore of transplantation of the gonads for rejuvenation, and especially for the restoration of sexual potency in senile individuals, Billings says is attended with such manifest lack of scientific experimental spirit and methods and is so tinctured with commercialism as to make this practice under present knowledge a professional disgrace. Substitutional organotherapy is embarrassed, too, by the difficulties attending the recognition and interpretation of the symptoms and signs due to the deficiency of the secretion of a single gland. These difficulties are intensified in the case of syndromes due to multiglandular deficiencies and in the necessary differentiation between the morbid conditions due to deficiencies of secretions of the internal glands and deficiencies in growth, development and other morbid condition due to want of sunlight and a properly balanced diet. At present, substitutional organotherapy in the treatment of conditions alleged to be due to deficiencies of the glands of internal secretion, with the exception of the thyroid and pancreas, cannot be utilized in general practice with the hope that definite results will be obtained. The brilliant results attending the use of preparations of the thyroid, including thyroxin, and of insulin afford reasonable belief that other

important glands of internal secretion will be found to yield active principles that will arm us with specific agents for the correction of morbid conditions due to deficiencies of secretion of the respective glands. In the meantime, recognizing our responsibility to the public in this as in other matters that affect the welfare of the people, we should not continue to patronize and support those manufacturers of glandular remedies who make statements of specific virtues possessed by pluriglandular preparations that are without foundation of fact. The existence and continued pernicious influence of the manufacturers of glandular products who publish statements of their therapeutic value without the support of established physiological and clinical facts will depend on whether the medical profession will patronize them. A decided forward step would be taken if physicians were to limit their use of animal organ preparations to those admitted to the United States Pharmacopeia and the current edition of New and Nonofficial Remedies.—Courtesy A. M. A.

The effect of endocrine feeding upon the learning performance of white rats. Blatz (W. E.) & Heron (W. T.), J. Exper, Psychol. (Lancaster), 1924, **7**, 291-311.

Blatz and Heron investigated the effects of feeding desiccated adrenal and pituitary substance (anterior lobe) to rats. The criteria of effects were solution of mazes and performance in problem boxes. The pituitary-fed rats were rather more, and the adrenal-fed rather less, efficient than the controls. The pituitary-fed showed slightly better growth. Reproduction was suppressed during the pituitary feeding.—R. G. H.

Endocrine therapy in infancy and childhood. Howland (J.), South. M. J. (Birmingham), 1924, **17**, 743-749.

Howland says: The conclusion is forced on us, and it is a conclusion to which physiologists and pharmacologists will subscribe, namely that if we use single extracts in pediatrics we are confined to the treatment of two conditions, thyroid deficiency and diabetes. Uniglandular therapy then is, in generel, unsatisfactory. Pluriglandular therapy has come into being on the supposition that not infrequently there is a disordered activity of several glands, a failure of coordination among them. For the belief that numerous glands may be affected in such ways as to produce various clinical syndromes there is no pathologic proof available. Similarly. there is no chemical or physiologic proof of the existence of such conditions. The fact that gradual improvement follows the administration of a heterogeneous mixture of gland extracts is not sufficient evidence to prove that a gland or group of glands is the cause of a clinical picture. One must demand a striking and almost immediate change. One must also demand pathologic or physiologic or chemical evidence. The clinician of the present day is in danger of

losing his clinical sense and his critical judgment. He leans too much on laboratory methods for his diagnosis.

—J. Am. M. Ass., 83, 1797.

Relation between the spleen and liver (Die Wechselwirkung zwischen Milz und Leber). Kobayashi (M.), Biochem. Ztschr. (Berl.), 1924, 151, 491-497.

Aceton is formed when sodium butyrate is perfused through the liver of guinea pigs. This is increased from two- to three-fold when extract of spleen is added. It is not affected by extract of the intestinal wall which contains cholin as does splenic extract.—F. S. H.

Blood calcium and the endocrine glands (Die endokrinen Drüsen und der Blutkalk). Leites (S.), Biochem. Ztschr. (Berl.), 1924, 150, 183-193.

In dogs and rabbits it was found that the normal blood calcium ranges within narrow limits and that the glands of internal secretion play an important rôle in its maintenance. The removal of the thymic and parathyroid function causes the blood calcium to decrease. The effect of thymectomy is slow in appearing; that of parathyroidectomy more rapid. When the thyroid and gonads are removed there is a tendency for the blood calcium to increase in amount. Opotherapy with thymus, thyroid and testicular preparations, which in the normal animal brings about no response, causes in the defective animal the return of the blood calcium to the normal level. Thymectomy in young dogs retards growth.—F. S. H.

The frequency of endogenous endocrine obesity and its treatment by glandular therapy. Lisser (H.), Calif. & Western Med. (San Fran.), 1924, 22, 509-513.

Overeating and insufficient exercise often cause exogenous obesity. The great majority of obese individuals are not fat for these reasons only. Hypothyroidism, hypopituitarism and hypogonadism are not uncommon, especially in mild degree, and are almost invariably characterized by adiposity. The importance of endocrine dysfunction in producing obesity directly, and in indirectly causing the symptoms that lead to obesity (abnormal appetite and physical inertia) should be recognized in diagnosis and in planning treatment. Basal metabolic rates are valuable, but not the sole index for institution of glandular therapy. A normal rate is not necessarily a contra-indication to the administration of thyroid extract, but its use should be checked by frequent rate determinations. Pituitary extract alone will sometimes reduce weight. Weighed diets are rarely necessary. Reasonable restriction of fats and carbohydrates is more practicable, less irksome, and usually suffices in conjunction with the proper endocrine therapy. The obesity of childhood and adolescence is usually of endocrine origin.

A case of Barraquer's disease (Un caso de enfermedad de Barraquer). Pardo, Endocrinol. & Nutrition (Madrid), 1924, **2**, 103-107.

The author describes a typical case of lipodystrophia progressiva in a girl of 14 years. Several endocrine symptoms were observed: hypogenital hands, asthenia, melanoderma in nose and cheeks, and amenorrhea. The basal metabolism was plus 10%. Pardo thinks that this syndrome ought to be called "Barraquer's disease," since Barraquer first described it.—E. B.

Metabolism observations in a case of urticaria scripta. Rowe (A. W.) & McCrudden (F. H.), Boston M. & S. J., 1924, **191**, 60-61.

A married woman of 36 presented the following abnormalities: marked anidrosis; lymphatic hyperplasia; itching skin; skin dryness; urticaria scripta; subnormal temperature; low pulse rate; low blood pressure; subnormal basal metabolism; albuminuria with rare casts but without impairment of renal function, and without increased non-protein nitrogen in the blood; slight secondary anemia; urine low in quantity, solids, and nitrogen; subnormal vital capacity, carbon dioxide in alveolar air, blood urea, and blood uric acid. With all the signs and symptoms pointing to disturbance in the sympathetic nervous system, and all of them such as have been described in cases of hypothyroidism, it seems probable that this case is one of endocrine imbalance with the thyroid chiefly involved. It is suggested that all such cases should be studied with this possibility in mind.—R. G. H.

Hormones and the pH. Zondek (H.) & Ucko (H.), Klin. Wchnschr. (Berl.), 1924, **3**, 1752-1753.

Zondek and Ucko tested the influence of thyroid extracts on the metamorphosis of tadpoles in various concentrations of hydrogen ions. They found a minimum between 7 and 7.7 pH (about the pH of the blood) and a marked action between 6.4 and 7. They believe that the hormones are inactive in blood because of its reaction, and are "tuned in" at the periphery by changes of the concentration of various ions, including hydrogen and hydroxyl. This may account for the difficulty in demonstrating biologically the presence of hormones in the blood.—J. Am. M. Ass., **83**, 1465.

The follicular hormone of the hen ovary. Allen (E.), Whitsett (J. W.), Hardy (J. W.) & Kneibert (F. L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 500-503.

The ovarian follicular hormone can be extracted from ovaries of laying hens. Injected into spayed rats it causes estrous growth in the genital tract. Extracts of full sized follicles, eggs from the oviduct, fresh eggs (also whites and yolks separately), and 5-, 10- and 14-day embryos with their membranes have given negative

results. These experiments establish the expected non-specificity of the follicular hormone as concerns birds and mammals.—J. C. D.

The physio-pathological significance of interstitial cells (De la signification physiopathologique des éléments interstitiels). Brugnatelli (E.), Arch. ital. di biol. (Pisa), 1922, 71, 120-132; see also, Folia gynaec. (Pavia), 1922, 15, 105-116.

Various observations on the so-called mast-lipoid cells, the interstitial tissue of the mammary gland, and the culture in vitro of the ovary indicate that the interstitial cells form part of a system of elements practically present in the whole organism, and capable of further development and multiplication under certain physiological and pathological conditions; in the author's opinion, however, their precise function is not known.—Physiol. Abst., 9, 362.

Glandular therapy: Physiology of the mammalian ovaries. Carlson (A. J.), J. Am. M. Ass. (Chicago), 1924, 83, 1920-1923.

Carlson asserts that at present there is no reliable evidence that ovarian extract effects are specific for the ovary. Until it has been conclusively shown in spayed females that these extracts prevent the atrophy of the uterus and initiate and maintain estrual periods typical for the species, it seems clear that experimental ovarian organotherapy has not been placed on a scientific basis. The reasons for the past failures may be inherent in the complexity of the ovarian hormones and their practical failure to be active when given by mouth; but the ovarian field can point to no such persistent and systematic work of hormone isolation as we have in the case of the thyroid and the pancreas. The sex life of the mammalian female is developed and maintained by the ovaries through continuous and temporary hormone mechanisms. Hormones acting more or less continuously develop and maintain the secondary sex organs and act to increase basal metabolism; temporary hormones from ripe follicles and corpus luteum initiate the estrual cycle, the early interaction between the fertilized ovum and the uterine mucosa, mammary gland hyperplasia and suppression of follicular growth. Menstruation appears to be only indirectly dependent on the follicular and luteal hormones, in that it follows failure of fertilization and atrophy of corpus luteum spurium. But the hormones initiating estrus are necessary precursors to menstruation. The initial cause in all menstrual disorders may be outside the ovaries and hence not to be affected by ovarian therapy. None of the ovarian hormones has so far been isolated, as determined by reliable biologic or chemical tests. And it is still an open question whether in the experimental animals any of the ovarian functions can be maintained by substitution therapy; that is, by feeding or injection of ovarian extracts.—Courtesy A. M. A.

New studies on folliculin. Passage of the hormones through the placenta (Nouvelles recherches sur la folliculine. Contribution à l' étude du pasage des hormones au travers du placenta). Courrier (R.), Compt. rend. Acad. d. sc. (Par.), 1924, **178**, 2192-2193.

Follicular liquid from the ovaries of the cow or sow, injected into guinea pigs, castrated (spayed) 8 months before and therefore in complete genital repose, caused within 48 hours the modifications of the vagina characteristic of heat, as shown by an active proliferation of the epithelial cells. One cc. of follicular liquid was injected into a pregnant guinea pig on each of the last 4 days of the term. A few hours after delivery one of the young was killed and examined histologically, when a rapid proliferation of the epithelial cells of the vagina was evident. Control animals showed no such vaginal activity. It is therefore concluded that the follicular hormone passes through the placenta.—Chem. Abst., **18**, 3067.

Sex reversal following ovariotomy in the fowl. Domm (L. V.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 28-35.

Both ovaries were removed from Brown Leghorn hens before egg laying began. The birds then came to resemble males in action and appearance. Autopsy showed masses at the ovarian site which on section proved to be immature testicular tissue.—J. C. D.

The extraction and some properties of an ovarian hormone. Doisy (E.), Ralls (J. O.), Allen (E.) & Johnston (C. G.), J. Biol. Chem. (Balt.), 1924, **61**, 711-727.

A method of extracting a hormone from the liquor folliculi which induces full estrous growth in the tissues of the genital tract is described. The yield in rat units from liquor folliculi is compared with the yield from other tissues. These results emphasize the physiological importance of the graafian follicle in the second cycle. A few properties of the hormone are given and data are cited to show that the activity of the follicular hormone is not associated with cholesterol color reactions.—F. S. H.

Influence of qualitative underfeeding on the function of the genital glands (Einfluss qualitativer Unternährung auf die Funktion der Keimdrüsen). Eckstein (A.), Arch. f. d. ges. Physiol. (Berl.), 1923, **201**, 16-24.

A diet deficient in fat, vitamin A, and phosphorus led to atrophy of testes and failure of spermatogenesis in male rats. The testes showed marked degeneration, which extended to the interstitial cells. The ovaries of female rats did not appear to be affected, though conception did not occur.—A. T. C.

A case of precocious puberty. Hutchinson (R.) & Wauhope (G. M.), Brit. J. Child. Dis. (Lond.), 1924, **21**, 57-62.

A girl of 3½ years of age began menstruating at 17 months and has been having irregular periods since then of the 28 day type, and lasting 2-3 days. She has pubic hair, which first appeared with the onset of menstruation, enlarged breasts, no axillary hair, a harsh voice, and is mentally bright and overgrown. She has no control over her bladder. No tumors were felt either on abdominal examination or by vaginal palpation of the ovaries. X-ray examination showed premature ossification of the skeleton and closure of the epiphyses; there was no indication of any tumor formation in the skull. The authors think the condition is due to ovarian hypersecretion, although they had no chance to prove their belief because of the refusal of the parents to permit operation.—M. B. G.

The relation of the female gonads to renal diabetes (Die Beziehung der weiblichen Keimdrusen zum renalen Diabetes). Küstner (H.), Arch. f. Gynäk. (Berl.), 1924, **122**, 282-309.

Clinical and experimental studies showed that renal diabetes occurs during pregnancy in both man and animals. This sensitivity of the kidneys disappears towards the end of pregnancy in human beings. Glycosuria occurs in non-pregnant women a few days before menstruation and in animals at estrus. Removal of the ovaries is followed by disappearance of renal diabetes. This does not occur when the uterus is removed. When ovaries from pregnant are implanted into non-pregnant animals there occurs a diabetes of one day. All these phenomena are interpreted as showing that renal diabetes is associated with a functioning corpus luteum.—F. S. H.

The effect of light doses of alcohol upon the estrus cycle and on number of corpora lutea and prenatal mortality in the mouse. MacDowell (E. C.), Proc. Soc. Exper. Biol & Med. (N. Y.), 1924, **21**, 480-485.

Mice were exposed to the fumes for 45 minutes each day, by enclosure in a pint milk bottle with a piece of filter paper soaked in 95% alcohol. It was concluded that the alcohol treatment had no effect upon the reproduction of the mice studied when judged by the following criteria: (1) age of opening of the vaginal orifice; (2) age at first estrus; (3) length of estrus cycle; (4) number of corpora lutea per ovulation; (5) prenatal and natal mortality; (6) number of living young per litter.—J. C. D.

Transplantation of the ovary in old animals (Innesti di ovaia in animali vecchi). Pettinari (V.), Boll. d. Soc. med.-chir. di Pavia (Milano), 1924, **36**, 163-169.

Preliminary note regarding two experiments. The first was carried out on a bitch about 17 years old, which showed all signs of senility, and in which the ovary of a young dog was transplanted endoperitoneally. A few months afterwards the bitch exhibited

remarkable phenomena of rejuvenation, including the reappearance of sexual activity. About 13 months after the operation she gave birth to 5 normal puppies, 4 of which she was able to suckle. The second experiment was carried out on a dog 12 to 13 years old, which also showed signs of advanced senility, and could hardly be made to move from its kennel. The ovary of a young bitch was grafted between the two layers of the tunica vaginalis, as suggested by Voronoff for the transplantation of the testis. A few months afterwards this animal likewise exhibited phenomena of rejuvenation, including the return of sexual activity.—Physiol. Abst., 9, 410.

Influence of ovaries on metabolism (Uber den Einfluss der Keim-drüsen auf den Stoffwechsel). Plaut (R.) & Timm (H. A.), Klin. Wchnschr. (Berl.), 1924, 3, 1664-1666.

In 5 cases women were sterilized by radiation. At the onset of amenorrhea the basal metabolism was depressed 100-300 calories but later returned to normal. The authors theorize to the effect that compensatory thyroid activity is ultimately set up.—R. G. H.

Osteomalacia in China. Wampler (F. J.), China M. J. (Shanghai), 1924, 38, 349-357.

This disease, which is common in North China, is attributed to dietary deficiency. Cures or great improvement in all cases were obtained by the use of cod-liver oil and calcium. The theory that osteomalacia is due to "a tropho-neurosis of ovarian origin" is considered to be untenable.—L. G. K.

Macrogenitosomia precox in a girl 9 years of age (Sindrome de macrogenitosomia precoz en una niña de nueve años). Burghi, Arch. espan. de pediat. (Madrid), 1923, 5, 257-271.

The patient, the daughter of an alcoholic father, after an attack of measles showed clearly defined hydrocephalus. She presented rachitic deformities in the thorax and lower extremities, cyanosis in the hands and feet and, ultimately, macrogenitosomia precox. Her height was 1.34 meters. The axillary hair and the mammary glands were completely developed. The author suggests that the macrogenitosomia is of epiphysial origin, but the deformity of the sella turcica, the symptoms of adolescent dystrophy and the adiposity seem to indicate that the normal function of the hypophysis is altered. The author is unable to explain the mechanism of the dystrophic phenomena provoked by the epiphysial tumors without the intervention of the incretory glands. This case in which there was no symptom of tumor suggests that the hypophysis had undergone precocious changes in consequence of the hydrocephalus and the accompanying intracranial hypertension upholds this interpretation.—E. B.

Contribution to the pharmacology of extracts of the posterior lobe of the pituitary gland. Kolls (A. C.) & Geiling (E. M. K.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **24**, 67-81.

The effects of intravenous doses of pituitary extract were studied in anesthetized and unanesthetized animals. In the unanesthetized dog the circulatory changes were: rise of mean blood pressure, decrease in pulse pressure, marked slowing of the cardiac rate even after vaginal influence has been removed by atropine, decrease in minute volume output of the heart, cardiac dilatation, paling of the skin and visible mucous membranes. The unanesthetized animals showed periods of apnea and marked reduction in consumption of oxygen. These changes were all less marked in the etherized animals. Immediately following the pituitary injection for a brief period the Hb. of the blood was increased.—G. E. B.

The diuretic and antidiuretic effect of pituitary extract and suggestions for a subsidiary test. Mackensie (W. G.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **24**, 83-99.

The inhibition of the flow of urine when collected from the bladder or lower ureter following pituitary injection is due to contraction of the smooth muscle of bladder or ureter or, with large doses, to a vascular effect on the kidney. The diuretic response is accompanied by a change in the distribution of water in the body but the hydremia outlasts the diuresis. The antidiuretic effect requires larger doses than that sufficient to produce diuresis but repeated small doses may have the effect of summation. It is not proved that the antidiuretic effect is produced elsewhere than in the kidney. A method of procedure for testing the diuretic properties of pituitary extract is given.—G. E. B.

Papilloneuritis in children with hypophyseal syndromes and their treatment by hypophysis and thyroid extracts (Algunas observaciones de papiloneuritis en niños con sindromes hipofisarios y su tratamiento por la hipofisis-tiroidina). Muñoz (U.), Union med. (Zaragoza), 1923, **250**, 97-99.

Two children with typical Frölich's syndrome and papilloneuritis were cured of the general syndrome and of the ocular lesions by administration of whole hypophysis extract alternated with injections of thyroid extract.—E. B.

Some factors concerned in the deterioration of pituitary extracts. Smith (M. I.) & McClosky (W. T.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 138.

Fresh infundibular lobes carefully dissected from pituitary glands removed soon after the animal is killed may be kept for at least 2 months at a temperature of -10 to -17 degrees C. without

loss of oxytocic activity, at about 0 degrees C their activity deteriorates rapidly after 2 weeks Extracts carefully prepared from fresh infundibular material or from standard powder and sterilized at 100 degrees C. were found to retain their oxytocic activity for one year when kept in a cold room, kept in the laboratory they showed no loss up to 8 months in either oxytocic or pressor activity. Temperatures of 45 to 60 degrees C cause deterioration The deterioration of pressor and oxytocic activities runs parallel This is regarded as contributory evidence of the chemical identity of the two principles —G E B

Insulin and diabetes insipidus (Insulina e diabete insipido). Villa (L.), Boll d Soc med -chir di Pavia (Milano), 1924, 36, 281-288.

The experiment was carried out on a patient who had been affected for years by diabetes insipidus due to a lesion of the pituitary body, and who had been repeatedly treated with pituitary extracts After the administration of insulin the polydipsia disappeared, and the quantity of urine eliminated in 24 hours fell from 12 to 2 litres The total blood volume grew during the first day of treatment, but diminished during the following ones. In spite of the simultaneous large administration of glucose the subject had two very severe hypoglycemic crises which lasted for many hours in spite of repeated injections of adrenalin The polyuria did not reappear when the insulin treatment was stopped, but it is not stated for how long —Physiol Abst 9, 393

Chemical regulation of the heart by the liver (Die chemische Regulation des Herzschlages durch die Leber). Asher (L) & Takahashi (K), Biochem Ztschr (Berl) 1924 149, 468-490

Apparently there is produced by the liver a hormone which acts upon the heart in the nature of a sympathetic stimulant —F S H

Diabetes accompanied by infantilism treated with insulin for a year (Diabète avec infantilisme traité de suis un an par l'insuline). Apert (E), Bull et mém Soc méd d hop de Par , 1924, 48, 894-895.

The patient was a young man The glucosuria was reduced from 200 grams to from 0 to 20-30 grams Growth was resumed in stature and weight, as was development of the sex organs —F S H

Observations on the use of insulin in nondiabetic children. Barbour (O.), Illinois M J (Oak Park), 1924 46, 131-133

The author has had apparently good results from the use of insulin in 12 nondiabetic children suffering with the following conditions· malnutrition, 2, malnutrition with tuberculosis, 2; malnutrition with chronic bronchitis, 3, marasmus 1 acute inanition, 1; acute nephritis, 2, normal infant 1 —I B

A practical danger in the use of insulin by the patient at home.
Berghoff (R. S.), J. Am. M. Ass. (Chicago), 1924, **83**, 1308-1309.

When insulin was first introduced, Berghoff recalls, it was
deemed advisable that its administration be begun with the patient
under hospital supervision.   When insulin therapy is prolonged
indefinitely, its administration by the patient himself becomes neces-
sary.   We have felt safe in assuring our patients who possess urine
sugar in appreciable amount that its entire absence on a given diet
and set insulin dosage bespeaks a corresponding satisfactory blood
sugar level, and calls for at least a temporary cessation of insulin
therapy.   In fact, we had almost accredited insulin with a gradual
resumption of carbohydrate tolerance.   However, at first sporadi-
cally, and of late regularly, we have been impressed with the unde-
niable fact that after a more or less continued course of insulin the
blood sugar threshold rises appreciably.   This rise of the blood sugar
threshold is of significant importance to the patient, robbing him of
his only check, and lulling him into a sense of false security.   If, for
example, before the initial use of insulin, a patient's blood sugar
threshold is determined at from 0.120 to 0.150, at which point sugar
appears in the urine, it has been our common observation that the
use of insulin soon raises those figures materially, in some instances
more than 0.50 point.   The practical significance is obvious.   If
patients are to be entrusted with the home use of insulin, a rough
check on their status is essential.   A daily blood sugar test is not
practical.   In the past we relied on a daily urine sugar estimation
to afford that information.   In view of the recent gross discrepancies,
however, between blood and urine sugar levels, that would seem
unsatisfactory.—Courtesy A. M. A.

Some effects of insulin on the carbohydrate and phosphorus metabo-
lism of normal individuals.   Blatherwick (N. R.), Bell (M.) &
Hill (E.), J. Biol. Chem. (Balt.), 1924, **51**, 241-259.

Insulin administered to normal subjects before glucose inges-
tion causes a marked decrease in the inorganic phosphorus of blood
plasma.   The rate of excretion of phosphorus in the urine is greatly
lessened at the same time.   These changes occur during the period
of hypoglycemia.   When insulin is superimposed upon a standard
diet the rate of excretion of phosphorus is altered to a large extent.
The relation of these findings to carbohydrate metabolism is dis-
cussed.   They bring additional support to the hypothesis that a
combination of hexose with phosphoric acid is an intermediate
product in the metabolism of carbohydrate.   The excretion of
normal urine sugar is not appreciably affected by the injection of
insulin.—F. S. H.

Studies of intermediary carbohydrate metabolism in the liver by
determination of the gas exchange (normal, hunger, insulin action

and pancreas deficiency) [Studien über intermediären Kohlenhydratumsatz an der Leber bei gleichzeitiger Verfolgung des Gaswechsels (Norm, Hunger, Insulinwirkung, pankreoprive Leber). VII.]. Brugsch (T.), Horsters (H.) & Shinoda (G.), Biochem. Ztschr. (Berl.), 1924, **151**, 318-334.

The respiratory quotient of the dog liver lies between, 0.51 and 0.68. In conditions of pancreatic diabetes the value ranges from 0.73 to 0.79. The oxygen need or consumption of the liver in the latter case is extraordinarily low, being but 1.0 per gram of protein, while that of the normal organ is around 2.2. Insulin in vitro increases the oxygen consumption of the liver but not up to the normal value.—F. S. H.

Intermediary carbohydrate metabolism in phloridzin diabetes during hunger and under insulin treatment (Studien über intermediären Kohlenhydratumsatz beim Phlorrhizindiabetes, im Hunger und unter Insulin. V.). Brugsch (T.), v. Exten (S.) & Horsters (H.), Biochem. Ztschr. (Berl.), 1924, **150**, 49-59.

Sugar formation in starved, phloridzinized animals is exhibited by the kidneys, liver and heart musculature; body musculature falls behind in this respect. The sugar is apparently derived from fat. Insulin does not seem to interfere in this process. Phloridzin diabetes differs from pancreatic diabetes in that in the former sugar is primarily formed in the kidneys, while in the latter the liver plays the major role. In the latter condition the ability to form sugar is not lost, but that of oxidation is. In the former condition (phloridzin diabetes) oxidative capacity is not necessarily lost, but the sugar-forming ability of the kidneys is heightened.—F. S. H.

A comparison of the rate of glycolysis in different bloods with special reference to diabetic blood. Cajori (F. A.) & Crouter (C. Y.), J. Biol. Chem. (Balt.), 1924, **60**, 765-775.

The rate of glycolysis in bloods of widely different sugar content incubated at 38° C. under sterile conditions was determined. It was found that the rate varies directly with the amount of sugar present, but that there is a marked deviation from the rate predicted by the monomolecular reaction velocity equation. No evidence was obtained which indicated a diminution of glycolytic power in diabetic blood. The effect of potassium oxalate in decreasing the rate of glycolysis has been found to be especially pronounced in diabetic blood.—F. S. H.

Atrophic sclero-gummous pancreatitis and syphilitic retro-peritoneal callosity (Pancréatite atrophique scléro-gommeuse et retro-péritonite calleuse syphilitiques). Carnot (P.) & Peron (N.), Bull. et mém. Soc. méd. d. hôp. d. Par., 1924, **48**, 1315-1318.

The patient showed almost complete destruction of pancreas but no diabetes.—F. S. H.

Insulin and phlorhizin glycosuria. Colwell (A. R.), J. Biol. Chem. (Balt.), 1924, **51**, 289-301.

Two experiments are described in which phlorhizinized dogs were kept running steady glucose excretions for 6 days each, finally completing the experiment in good physical condition. These dogs were given injections of iletin, three in all, with resultant depressions in the output of sugar.—F. S. H.

The influence of insulin on phlorhizin poisoning. Cori (C. F.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 99-106.

Insulin causes a fall in blood sugar in completely phlorhizinized rabbits, but the power of blood sugar regulation is not lost. A marked diminution in the sugar excretion is brought about. Sugar formation from proteins is not affected and the nitrogen excretion is not diminished.—G. E. B.

Comparative study of the sugar concentration in arterial and venous blood during insulin action. Cori (C. F.) & Cori (Gerty T.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 72-73.

Glucose was injected into rabbits and simultaneous samples of blood from the femoral artery and vein were analyzed to find how much glucose had been absorbed by the muscles. Then insulin was added to the glucose solution injected. The 8 observations reported show an average increase of nearly 60% in the amount of glucose absorbed.—J. C. D.

Insulin from the codfish. The direct application of picric acid to the islet tissue. Dudley (H. W.), Biochem. J. (Liverp.), 1924, **18**, 665-668.

A convenient method of extracting insulin from the islet tissue of the codfish is described. It consists of applying picric acid directly to the tissue, extracting the insulin-containing picrate fraction with watery acetone, and converting the picrate into a soluble hydrochloride as described in a previous paper. From the islet tissue of the cod, although collected from fish which had been caught at varying intervals up to 24 hours previously, a yield of about 12 rabbit units per gram of tissue was obtained. The islet tissue of the cod contains, weight for weight, apparently ten times as much insulin as does mammalian pancreas.—F. S. H.

The action of insulin on different carbohydrates (Recherche au sujet de l'action exercée par l'insuline sur les différents hydrates de carbone). Enselme (J.), Thèse de Lyon, 1924; abst., Presse méd. (Par.), 1924, **32**, 752.

In this research, carried out under the direction of Hugounenq, the author studied the chemical composition of insulin and its effect on various carbohydrates. Using insulin prepared according to the method of Chabanier (the activity of which was verified on rabbit), a crystallized body was obtained which had no effect on glycemia. The investigations of Hugounenq and Enselme show that the direct action of insulin in vitro on carbohydrates is negative. Negative results were likewise obtained when the reaction was made in the presence of blood serum or organ extracts, such as liver or lung. On the contrary, insulin modifies the action of certain blood ferments. For instance, it clearly increases the activity of maltolytic ferment. It acts irregularly on glycolytic ferment and has no influence on the ferments which act on dextrin and glycogen. Incidentally, Hugounenq and Enselme noted a ferment in the blood which hydrolyzes insulin. These studies show that although insulin does influence carbohydrate metabolism, its action is very complex and its mechanism is still difficult to follow.—R. G. H.

The action of pepsin on insulin. Epstein (A. A.), Proc Soc. Exper. Biol. & Med. (N. Y.), 1924, 22, 9-11.

A mixture of insulin and pepsin was acidified. This when tested by injection into animals showed no insulin activity. Activity can be restored by proper neutralization even though the mixture has stood for 4 days at body temperature. Pepsin, therefore, does not digest insulin but inactivates it in some other way.—J. C. D.

The relation between the pancreas and the carbohydrate metabolism of muscle. I. The effect of extracts from the gland on lactic acid production in vitro. Foster (D. L.) & Woodrow (C. E.), Biochem. J. (Liverp.), 1924, 18, 562-575.

The presence in the pancreas of a factor which is capable of causing a marked inhibition in lactic acid production of chopped muscle is shown. This inhibitory factor is neither trypsin nor insulin and probably not antiglyoxalase. A method is described for making a stable preparation of the pancreas with all its enzymes intact, and details are given for making an extract of this preparation with 70% alcohol which contains the inhibitory factor in high concentration.—F. S. H.

The blood sugar reducing properties on plant extracts and oxydases together with the proof of enzymes in insulin (Ueber die blut-zuckerherabsetzende Wirkung vom Pflanzenextrakten und Oxydasen sowie den Nachweis von Fermenten im Insulin). Glaser (E.) & Wittner (L.), Biochem. Ztschr. (Berl.), 1924, 151, 279-305.

Substances which cause a lowering of blood sugar in rabbits

were extracted from fungi (mushrooms) and turnips. The extract of the former obtained by the use of acid-alcohol was inactive. It is possible that a part of this activity is attributable to oxydase enzymes present in the original material. Such oxidizing enzymes were demonstrated in insulin. Peroxydase and aldehydase in particular were shown. These same enzymes were found also in the liver, pancreas and muscles.—F. S. H.

The influence of insulin on the respiratory metabolism of normal rabbits. Hawley (Estelle E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 66-67.

The author concludes that insulin, when administered to normal animals, brings about first a slight decrease, then a decided increase in the R. Q. curve, reaching the peak 2 hours after injection and returning to the basal level 4 hours later. A blood sugar drop accompanies the R. Q. change, the lowest blood sugar occurring at the peak of the curve. The return to normal is less rapid than the return to normal of the R. Q., though the curve is well on its return by the end of the 4 hours. There is, in the second hour, both a decrease in the O_2 and an increase in the CO_2, both changes tending to increase the R. Q. The O_2 consumption and the heat production would indicate that the total metabolism is not markedly increased.
—J. C. D.

Diabetes in an infant treated with insulin with severe cutaneous reactions (Un cas de diabète infantile traité par l'insuline avec accidents cutanés graves: l'erythrodermia édémateuse insulinienne). Lereboullet (P.), Lelong (M.) & Frossard (R.), Bull. et mém. Soc. méd. d. hôp. de Par., 1924, **48**, 1189-1190.

The infant received early in the insulin treatment for its diabetes preventative inoculations for rugeola and diphtheria. About a week later urticarial lesions appeared half an hour after the injections of insulin. Five days later this became complicated by a generalized edematous condition. Withholding of insulin was followed by recession of the urticaria and edema. Renewal of insulin administration resulted in reappearance of the cutaneous disorders. Later rugeola came on and was recovered from, but the cutaneous reactions to insulin continued up to the time of death.—F. S. H.

Vomiting of pregnancy with acidosis treated by insulin (Un cas de vomissements gravidiques à caractére incoercible avec état d'acidose très prononcé et traité par l'insuline). Lequeux, Weill (A.) & Laudat, Gynéc. (Par.), 1924, **23**, 408-409. See also: Bull. d'obst. et de Gynèc. (Par.), 1924, **13**, 348-355.

Favorable results are reported using 10 units of insulin. Recurrences occurred, but they were amenable to additional insulin administration.—F. S. H.

The pharmacological assay of insulin. MacLeod (J. J. R.), & Orr (M. D.), J. of Pharmacol. & Exper. Therap. (Balt.), 1924, **23**, 137-138.

Rabbits starved for 24 hours were used. Originally one unit of insulin was defined as that amount which would lower the blood sugar of a normal rabbit to the convulsive level (0.045%) in 5 hours (physiological unit). This unit has been changed to one-third of the original unit (clinical unit). To make the definition inclusive and to allow for the duration of the hypoglycemia as well as the varying weight of the animals, the following equation is used:

$$\text{units per cubic centimeter equals } \frac{a}{b} \times \frac{w}{c} \times 1.5;$$

"a" is the difference between the normal blood sugar and the average of the blood sugars at 1½, 3 and 5 hours after injection; "b" is the difference between the normal blood sugar and 0.045; "c" is the number of cubic centimeters of insulin injected, and "w" is the weight of the rabbit in kilograms. The factor 1.5 is used because the original unit was based on the effect produced in the rabbit weighing 2 kgm., and the clinical unit is one-third the physiological. The method of carrying out the assay is given.—G. E. B.

The significance of glycosuria. Marsh (P. L.), J. Lab. & Clin. M. (St. Louis), 1924, **9**, 663-674.

Glycosuria should lead to the suspicion of diabetes mellitus until proved otherwise. It must be remembered that there are other syndromes of which glycosuria is a constituent. Whatever the mode of treatment adopted in a case of diabetes, it is of primary importance that the diabetic be kept in a sugar-free state.—I. B.

The perlingual administration of insulin (Uber die perlinguale Applikation des Insulins). Mendel (B.), Wittgenstein (A.) & Wolffenstein (E.), Klin. Wchnschr. (Berl.), 1924, **3**, 470-472.

When a solution of insulin is placed in the mouth, the active constituent is absorbed and exerts its customary action on carbohydrate metabolism. The practical significance of this discovery is far reaching because if this mode of application should prove to be universally successful, the disagreeable hypodermic administration could be done away with.—Chem. Abst., **18**, 3219.

Behavior of the blood sugar in the rabbit under various conditions and its distribution in the blood (Ueber das Verhalten des Blutzuckers beim Kaninchen unter verschiedenen Bedingungen und über seine Verteilung im Blut). Mochizuki (N.), Biochem. Ztschr. (Berl.), 1924, **150**, 123-143.

When the pancreatic duct is tied off in rabbits the blood sugar rises and then falls after a few days. It rises again and tends to maintain this condition. The first rise has its origin in a flooding of the blood and tissues with diastase and the glycogen breakdown therewith connected; the second is attributable to the gradually developing sympathicotonic condition. The same behavior is exhibited in experimental animals after glucose administration. Adrenalin injection into the experimental animal produces a like reaction, e. g., increased rise in blood sugar and a delayed fall. In the normal animal 25% of the blood sugar is found in the corpuscles and 75% in the plasma. In the experimental animal the corpuscular sugar content rises to 43% and then falls to the original value, without rising again. The increase in blood sugar which takes place in the normal animal after pilocarpin injection is inhibited in the operated rabbit. Phloridzin administration is followed by a fall in blood sugar in the animal with the pancreatic duct tied off.—F. S. H.

Insulin and the skin. Müller (E. F.) & Corbitt (H. B.), J. Lab. & Clin. M. (St. Louis), 1924, 9, 608-617.

Experimenting on rabbits, the authors found that there is a decided difference between the results of subcutaneous and intradermal injections of insulin. The effect of insulin is considerably prolonged if given by the intradermal route. Fatal doses with the intradermal route may be higher than fatal doses by the subcutaneous.—I. B.

The normal value of the threshold for sugar excretion (Ueber den normalen Wert der Zuckerausscheidungsschwelle). Nakayama (M.), J. Biochem. (Japan), 1924, 3, 407-422.

The threshold for sugar excretion in non-diabetic, healthy and diseased persons ranged from 0.08 to 0.21%, with the maximum number of cases falling between 0.13 and 0.19%. Values below 0.12 and above 0.20 were rarely encountered. No marked differences were found between the diabetics and the non-diabetics, though it must not be overlooked that higher values were the rule in the former and lower in the latter. Sex seems to have no influence on the value; but age does in the sense that there is a tendency for the values to increase with age.—F. S. H.

Experiences with insulin treatment in childhood (Erfahrungen über Insulinbehandlung im Kindesalter). Priesel (R.) & Wagner (R.), Ztschr. f. Kinderh. (Berl.), 1924, 38, 103-117.

Severely afflicted diabetics must undergo protein restriction even with insulin. Blood sugar determinations are necessary in childhood. In diabetic coma large doses of insulin and glucose and liquids are indicated. The danger of overdosage with insulin is greater in childhood than in adulthood. The carbohydrate toler-

ance of the person may be raised by insulin treatment if the disease has not progressed too far   The intoxication following overdosage with insulin is quite similar to the picture produced in Rowntree's "water intoxication."—Am J Dis Child , **28**, 633.

Diabetic coma with pulmonary tuberculosis treated with insulin (Coma diabetique et tuberculose pulmonaire.   Traitement par l'insuline). Rathery (F) & Dreyfus-Sée , Bull et mém. Soc. méd. d. hôp. de Par., 1924, **48**, 973-979

A case report in which the following points are emphasized: 1. rarity of coma in a tubercular diabetic; 2 complete cure of the coma by insulin for 3 months; 3 The lack of association between excretion of acetone bodies and beta-oxybutyric acid; 4 the need for large doses of insulin —F. S H

The production of lactic acid in diabetes following the administration of insulin. Tolstoi (E), Loebel (R O), Levine (S. V.) & Richardson (H B), Proc Soc Exper Biol & Med. (N. Y.), 1924, **21**, 447-452.

Four patients with uncomplicated diabetes were studied   The results were contrasted with those obtained with 4 non-diabetics who were injected with adrenalin   It was concluded that both extracts lower the inorganic phosphate of the blood   Extreme drops in blood sugar may occur with no change in the lactic acid concentration.   Increases in lactic acid were observed only when insulin hypoglycemia was produced   Lactic acid increases with adrenalin hyperglycemia.   Insulin causes an increase in the respiratory quotient beyond what can be accounted for by the production of lactic acid.   This is evidence of the stimulating action exerted by the extract on the oxidation of carbohydrate —J C D

The effect of insulin upon the rate of fermentation of glucose by yeast. Travell (J. G) & Behre (J A), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 478-479.

Insulin fails to influence the rate of fermentation.   The action of insulin in the body is, therefore, probably not upon the glucose molecule itself.—J C. D

Does the pancreatic hormone (insulin) lower the blood pressure? Weinberger (W) & Holzman (A), J Am M Ass. (Chicago), 1924, **83**, 1215-1216.

In the course of treatment of patients with diabetes mellitus, Weinberger and Holzman made the following observations: 1. Under insulin administration, a number of diabetic patients with hypertension showed a diminution in blood pressure.   2. Some with a normal or low blood pressure exhibited a still further lowering. 3. The factor of blood sugar reduction is independent from the factor of blood pressure reduction, since many lowered blood pres-

sure readings were obtained though the blood remained hyper-glycemic on account of the diet being adjusted to that effect. Four cases are here cited. The capacity of insulin to reduce the blood pressure under certain conditions was also observed by Klemperer and Strisower, who obtained similar, though not identical, experimental results. The authors raise the question: Does not insulin, representing, as it does, the internal secretion of the pancreas (if there should be an etiologic relationship between it and the lower blood pressure observed), act in conformity with the hypothesis of an antagonistic action between the hormones of the pancreas and suprarenal glands? That the height of the blood pressure bears some relationship to the concentration in the circulating blood of the suprarenal hormones is now generally recognized. Therefore, the administration of insulin should have a tendency to lower the blood pressure, which should occur the more easily in conditions with hypofunction of the suprarenal glands, so that a syndrome analogous to Addison's may result.—Courtesy A. M. A.

A crystalline substance from the parathyroid glands that influences the calcium content of the blood. Berman (L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 465.

The substance, extracted from ox parathyroids with acidified alcohol, produced a definite increase in the calcium content of the blood when injected into the circulation. No report on methods or experimental evidence is given.—J. C. D.

On the efficacy of various calcium salts in parathyroid tetany. Compere (E. L.) & Luckhardt (A. B.), Proc. Soc. Exper. Biol. & Med (N. Y.), 1924, **21**, 526-528.

Calcium carbonate, nitrate or acetate may be substituted for calcium lactate to prevent tetany in dogs. The carbonate is more constipating than the lactate, while the other two are irritating to the gut. Soluble calcium phosphate is irritating, produces untoward symptoms and seems even to increase the tetany.—J. C. D.

The present position of parathyroid therapy. Critchley (M.), Practitioner (Lond.), 1924, **113**, 56-62.

The author reviews briefly our knowledge of the parathyroid and takes up the conditions in which parathyroid treatment might reasonably be supposed to be of value. He found in personal practice that it was useful in treating paralysis agitans, particularly the senile type, in varicose ulceration of the leg and in Graves' disease. It had a slight influence in reducing the intensity of the paroxysms in whooping cough. Warning is given of the danger of over-dosage.—J. C. D.

Experimental tetany and diet. Inouye (T.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **22**, 49-51.

In dogs following thyroparathyroidectomy, lactose in large quantities helped protect the animal from tetany. Tetany was invariably associated with low blood calcium and there was a parallelism between the lowering of the calcium and the severity of the symptoms. The author regards this change in calcium as secondary to "a complicated disturbance of metabolism in which protein metabolism plays some role."—J. C. D.

Increased gastrointestinal permeability as a possible factor in parathyroid tetany. Luckhardt (A. B.) & Compere (E. L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 523-526.

Increased permeability of the gut to the toxic products producing tetany might explain the attacks following parathyroid removal. Dogs, which have recovered from the acute effects of parathyroidectomy, can be thrown into tetanic convulsions by doses of croton oil or cascara or sulphur ointment. This indicates that increased permeability of the gut from whatever cause is a factor in producing convulsions. The authors point out the danger in the light of these results of giving violent cathartics in epilepsy.

—J. C. D.

Autoplastic and homoplastic parathyroid transplantation. Swingle (W. W.) & Nicholas (J. S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 429-433.

Tables showing experimental results on 34 cats are given. Homoplastic grafts were unsuccessful, while the autoplastic persisted and seemed to give some protection against tetany.—J. C. D.

Recent investigations on tetania parathyreopriva and idiopathic tetany and on the functions of the parathyroids. Paton (N.), Edinb. M. J., 1924, **31**, 541-559.

The author discusses 59 papers published since 1916. He concludes that the increased muscular tone which generally follows removal of the parathyroids indicates that these structures exercise an influence upon the tonus of skeletal muscles. The marked increase of muscle tone and the close similarity of the other symptoms to those produced by removal of the parathyroids which follow the administration of guanidin and its methyl compounds seem to show that they play a part in the maintenance of that tone. The fact that these substances are increased in the blood and urine after parathyroidectomy, and in the urine in idiopathic tetany, suggests that their metabolism is controlled by the parathyroids and that it is through them that muscular tone is regulated. The immediate action of these substances in one adequate dose is undoubtedly to

stimulate the efferent neurons of the spinal cord, and in a moderate dose to increase the excitability of the neuro-myons. But with repeated doses they apparently become anchored upon these structures to produce a condition of facilitated activity, and this is probably their chief mode of action in tetany. That a decrease in the calcium of the blood is not the primary factor in the causation of the symptom is shown by the effect of bleeding and transfusing a calcium-free solution, and further by the fact that a decrease in the calcium of the blood may occur without tetany, e. g., in uremia, and that tetany may occur without a marked fall in the calcium. There is no conclusive evidence to show whether this fall, when it occurs, is a result of the increase in the methyl-guanidin or a concomitant of it. No satisfactory explanation of the rise in the phosphates has been given, although the results of Greenwald and György indicate that there may be a decreased excretion. There is no indication that the increase in the phosphates plays a direct part in the production of symptoms. Accepting the evidence that the parathyroids influence the tone of muscles, they seem to do so by controlling the metabolism—production or destruction, or both—of the methyl-guanidins. Evidence has been adduced that methyl-guanidins and creatin may be derived from the cholin of the lecithin molecule. There is some indication that an excess of guanidins may be detoxicated by conversion to creatin. There seems to be no doubt that the precursors of the methyl-guanidins are endogenous, although possibly the products of the digestion of meat, etc., may also furnish precursors.—J. C. D.

Regeneration of the thymus following double suprarenalectomy in the rat. Jaffe (H. L.), J. Exper. M. (Balt.), 1924, 40, 325-342.

In this paper is presented evidence that close interrelationship exists between the thymus and suprarenal glands in the rat. The data consists of protocols from 66 double suprarenalectomized rats of varying ages and 21 controls. It was found with great consistency that the removal of the suprarenals resulted in hyperplasia of the thymus in adult rats. The enlargement which was at its maximum after 3 to 5 weeks was more pronounced in the female than in the male. This effect on the thymus is believed to result from a disturbance of the interrelations between the gonads, the thymus and the interrenal glands. A possible relationship between the thymic enlargement of Addison's disease, exophthalmic goiter and status lymphaticus and that following double suprarenalectomy is suggested.—I. M.

Direct evidence of regeneration of the involuted thymus following double suprarenalectomy in the rat. Jaffe (H. L.), J. Exper. M. (Balt.), 1924, 40, 619-625.

A portion of the thymus was removed in each of 13 old rats

for a control and 13 to 17 days later bilateral suprarenalectomy was performed. The histological appearance of the remaining thymus tissue several weeks after suprarenalectomy was then compared with that of the thymus before this operation. In control animals in which the effect of partial thymectomy alone was studied, no regeneration was observed. However, regeneration after suprarenalectomy was found to occur with striking constancy. The maximum degree of regeneration appeared within two weeks after the suprarenalectomy.—I. M.

Influence of thymus upon skeletal growth as shown by tissue culture and extirpation methods (Uber den Einfluss des Thymus resp. dessen Extraktes auf das Knochenwachstum studiert sowohl durch Gewebskultur als auch durch Extirpationsversuch). Katsura (H.), Mitt. a. d. med. Fakult. d. k. Univ. zu Tokyo, 1922, 30, 177-206.

Removal of the thymus is comparatively easy in birds because the gland lies quite outside the thorax. Extirpation of the thymus in young birds is followed by a rapid differentiation and early attainment of adult characters. Birds from which the gland has been removed show a lower calcium content in bones and the females lay eggs with less calcium than normal in the shells. When added to tissue cultures, in which it is unaided or unopposed by other incretory glands, the thymus accelerates growth.—W. J. A.

The influence of thyroidectomy, gonadectomy, suprarenalectomy and splenectomy on the thymus gland of rabbits. Marine (D.), Manley (O. F.) & Bauman (E. J.), J. Exper. M. (Balt.), 1924, 40, 429-443.

The data were obtained in a comprehensive study of the effects on the remaining tissues of the body after the various operations mentioned in the title. The results presented were taken from 373 completed protocols in which the thymus and the lymphoid tissues were studied. Thyroidectomy hastens while gonadectomy delays involution of the thymus. Suprarenalectomy not only delays involution but even causes regeneration of both thymus and lymphoid tissue. Thyroidectomy prevents this reaction even with combined suprarenalectomy and gonadectomy. Combined suprarenalectomy and gonadectomy is more effective than either alone and causes a true lymphoid and thymus hyperplasia. This causes a syndrome resembling status lymphaticus and is thought to be independent of any chromaffin tissue deficiency. Thymus and lymphoid hyperplasia in infancy are believed to be manifestations of interrenal and gonad functional underdevelopment. The so-called lymphatic constitution which underlies or accompanies exophthalmic goiter, Addison's disease and acromegaly is thought by the authors to be dependent upon a partial suppression of certain functions of the interrenal and sex glands.—I. M.

The thymic constitution. Schridde (H.), München. med. Wchnschr., 1924, **71**, 1533-1534.

Schridde has encountered since 1914 five new cases of hyperplasia of the medulla of the thymus in new-born boys. The infants were fat and excessively large (one of them measured 61 cm.). He emphasizes the significance of the hyperplasia of the thymus medulla. The combination of the swelling of the follicles of the spleen and the intestines, the abnormal height, and the abundance of fat occurs only with this form of thymus hyperplasia.

—J. Am. M. Ass., **83**, 1961.

The thymus gland in the Chinese. Shellshear (J. L.), China M. J. (Shanghai), 1924, **38**, 646-657.

The cervical portion of the thymus gland of the Chinese is well marked, and is represented by two distinct lobulated extremities which reach, and in some cases pass under, the thyroid gland. Microscopic examination shows that regressive changes are later here than elsewhere, and the gland is therefore cervico-thoracic in the Chinese, whereas in the adult European it is mostly a thoracic structure. Of 100 subjects, examined post-mortem, varying from 12 to 87 years of age, 11 had glands that were abnormally large (group 1), including 2 over 30 years of age. Group 2 contained 40 subjects, and the glands of these weighed from 35 to 40 grams; group 3 (medium size) contained 23; group 4 (gland small) contained 14; and group 5 (gland insignificant) had 8. The thymus was absent in 4. It is thus evident that the gland is both larger and more persistent than in the European. Microscopic examination showed the large size to be due to thymic tissue. An abundance of parenchyma is held until a later age than in the European. A rather far-fetched theory of sexual selection of a thymic type is offered as an explanation of the facts observed. A more plausible suggestion is also made that the persistent thymus might be acquired in the Chinese, due to frequent exposure to infection.

—L. G. K.

Endocrine origin of thymic asthma. Werneck (C.), Deutsche Ztschr. f. Chir. (Leipz.), 1924, **187**, 133-138.

A male infant, aged 3 months, had had stridor from birth, and was unable to nurse properly on account of disturbance in respiration. The clinical picture was that of thymic asthma, with spasms of cyanosis and intense dyspnea lasting for 2 hours and followed by a profuse flow of mucus. The thymus did not seem to be enlarged, and there was nothing to indicate disease of the bronchial or tracheal glands. The stridor accompanied both inspiration and expiration; the lower ribs were drawn in as inspiration began and then were protruded. Werneck proposed thymectomy but the family declined. The child was brought in asphyxiated a few days later,

in deep cyanosis and apparently dead. Without any attempt at anesthesia the right lobe of the thymus was removed. It weighed 5 gm. and was macroscopically normal, but the microscope revealed histologic changes. The total weight of the thymus can be estimated at 9 gm., which is within normal range, and there could not have been compression of the air passages or nerves. All the symptoms gradually disappeared, the stridor the second day. There has been no tendency to suffocation or cyanosis since the fourth day, and the child in 2 months had gained 1,200 gm. These facts can be explained only by assumption of excessive endocrine functioning of the thymus as responsible for the respiratory disturbances, cured by partial thymectomy.—J. Am. M. Ass., **83**, 1380.

The thyroid and specific dynamic action. Preliminary report. Baumann (E. J.) & Hunt (L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 447-448.

Six rabbits were used. The increased heat production found normally following the ingestion of glucose does not take place in the absence of thyroid tissue. Some specific dynamic action results, however, if even a small amount of thyroid (1/20 of the normal) is present and physiologically active.—J. C. D.

Prophylaxis and treatment of goiter by iodine (Profilaxia y tratamiento del bocio por el iodo). Bonilla, Med. ibera (Madrid), 1923, No. 317, 456-459.

The theory which seeks to explain the cause of goiter as due to absence of iodine in the food is today conceded to be of great importance. Although it has not been completely proved which of the many current theories is correct, it is undoubtedly true that iodine plays a very important part in the normal physiology and pathology of the thyroid, and this fact forms the basis of the modern prophylaxis and treatment of goiter. Good results are obtained from the use of iodine in sporadic goiter of the adult, being principally advocated in diffuse goiter, although it is possible to secure good results in cases accompanied by small nodular formations. Small doses should be used—3 mg. daily for 75 days, or once or twice per week for several months. There is danger in this medication of causing Basedow's disease, although this is very rare with the doses and care employed at present. Basedow's disease is more or less easily produced according to the region. In Spain it is quite frequent, especially in the goitrous regions. In spite of the fact that some advise iodine therapy even in Basedow's disease, Bonilla agrees with the majority of investigators that iodine is contraindicated when there exist the slightest symptoms of hyperthyroidism and that it ought to be employed in the prophylaxis and treatment of goiter only in very small doses.—G. M.

Certain pathological tissue changes in thyroidectomized sheep. Gold-
berg (S. A.) & Simpson (S.), Proc. Soc. Exper. Biol. & Med.
(N. Y.), 1924, 21, 567-568.

Several thyroidectomized lambs showed subcutaneous and sub-
serous edema, ascites, hydrothorax, parenchymatous nephritis and
aortic changes. The last occurred both in the systemic and pul-
monary aortas and consisted of degeneration and calcification of the
media in the form of placques. Some or all of these changes
appeared in 5 of 10 animals from 8 months to 2½ years after
operation. Twin controls were healthy.—J. C. D.

Production of goiter in rats by restricted iodine feeding. Hayden
(E. M.), Wenner (W. T.) & Rucker (C. W.), Proc. Soc. Exper.
Biol. & Med. (N. Y.), 1924, 21, 546-547.

Rats fed an iodine-poor diet showed thyroids averaging twice
the size of those in the controls whose drinking water contained
0.1 mg. of iodine per liter. Six experimental and six control ani-
mals were used.—J. C. D.

The action of thyroid and iodine preparations fed to frog larvae.
(Zur Fütterungswirkung von Schilddrüse und Jodpräparaten auf
Froschlarven). Kahn (R. H.), Arch. f. d. ges. Physiol. (Berl.),
1924, 205, 404-414.

Various effects were produced by feeding different thyroid prep-
arations, thyroid derivatives, and iodine preparations—from rapidly
developing malformations and death on the one hand to mild effects
resulting after a longer time through accelerated metamorphosis in
non-malformed dwarfs, depending essentially on the differing
amounts of iodine administered. Thyroids from subjects of Graves'
disease produce much less effect than normal glands. Venous blood
from dog thyroids produces no demonstrable effect. Antithyreoidin
(Moebius) does not inhibit the effect of small doses of thyroid.
Feeding the body substance of frog larvae at the height of the
thyroid effect on them has no effect on other larvae so fed. Thyroid
effect varies with the diet fed, as stated by Jarisch, but only under
special experimental conditions. Of various commercial artificially
iodized products tested only iodalbacid and iodglidin were effective.
Iodine tincture fed with meal has a marked influence on growth and
metamorphosis. Hence it would appear that the effectiveness of
thyroid and of iodine compounds depends on special types of iodine
linkage in the molecule, and not on iodine action per se.—A. T. C.

IS THERE AN ANTAGONISM BETWEEN THE MALE AND THE FEMALE SEX-ENDOCRINE GLAND?

ALEXANDER LIPSCHÜTZ

Institute of Physiology, Dorpat University
TARTU-ESTONIA

The suggestion of Steinach that an antagonism exists between the male and the female sex glands has been discussed by different authors. Recently Moore, basing his opinion on the experimental work of himself and of his pupil Fisher, came to the conclusion that the assumption of an antagonism has to be rejected (1).

Experimental work which I have done during the past two years with my coworkers, first with W. Krause and H. E. V. Voss, later on with F. Lange, M. Tiitso, H. Perli and D. Svikul, made it evident that the position as held by Moore is by no means justified.

First of all Moore does not discriminate between two different meanings of "antagonism." Steinach spoke of an antagonism of the sex glands in the sense that the taking and the survival of the heterosexual graft is inhibited by the glands in situ. According to Steinach the taking and the survival of the heterosexual graft is possible only when the glands in situ are removed and, as in his experiments with hermaphroditism, reengrafted simultaneously with the heterosexual gland. Sand succeeded in producing experimental hermaphroditism engrafting the ovaries in the testicles in situ, thus injuring the latter

to a certain degree. But Schultz, Moore and Fisher have shown that both taking and survival of the opposite-sexed graft is really possible when one or even both uninjured glands in situ are present. But on the other hand, Steinach suggested that there is an antagonism in the sense also that the sex gland inhibits the characters of the opposite sex by its sexual hormones. As to the second meaning of antagonism the numerous experiments of Goodale and Pézard which have been fully confirmed by Zawadowsky, have shown that such an inhibiting influence really exists (plumage, spurs). This affords, as I think, another possibility of antagonism, i.e., that the heterosexual graft survives, but that its *hormonic effect* is inhibited by the glands in situ. Our own experiments have shown that the last supposition is true.

In the following paragraphs are reported the new data we have obtained in experiments on hermaphroditism in guinea-pigs. Only part of this work has as yet been published (2). Detailed papers are in course of publication.

(1)   Ovarian and testicular fragments survive for several months, even in presence of two glands of the opposite sex, and can perform their endocrine function.

(2)   But possibility of survival does not mean that the presence of the heterosexual glands is of no influence   This is best shown by two comparative series of experiments: (a) Out of sixteen animals into which one to two ovaries were engrafted by the intratesticular method of Sand, both testicles remaining in the body, only four revealed a feminine hormonic effect (hypertrophy of the mammary glands and nipples), whereas six experiments with intratesticular ovarian grafts and unilateral testicular castration revealed a feminine hormonic effect *without any exception*.   (b) Seventeen male guinea pigs with testicular fragments were engrafted intrarenally with ovarian fragments (from one-fourth to two ovaries); all of these animals, with one exception, revealed a feminine hormonic effect.

(3)   Fourteen guinea pigs were engrafted with ovaries by the intrarenal method, both testicles remaining in situ; there was not a single case with a feminine hormonic effect, though the animals were observed sometimes more than five months.

It suffices to compare the result in 2b with that in 3 to understand how great is the influence of the testicle in situ on the hormonic effect of the ovarian graft. But still more evidence is given by the experiments mentioned in paragraph 4.

(4) The left ovaries of five guinea pigs were engrafted by the intrarenal method into five males having both testicles in situ; the right ovaries of the same females were engrafted by the same method into five males which were of the same age as the first group, but had previously undergone partial castration, only testicular fragments being now present in the body. No animal of the first group revealed a feminine hormonic effect, whereas all the animals of the second group did. Here the ovary of the same female was capable of producing a striking hormonic effect when the testicle was reduced to a fragment, but was unable to do so when both testicles were present.

(5) The antagonistic influence exhibited by the testicle is evident even in those cases in which the hormonic effect of the ovarian graft is not definitely inhibited. In the intratesticular experiments of Sand and of Krause with both testicles remaining in the body, the *time of latency,* i. e., the time between ovarian transplantation and the beginning of the feminine hormonic effect, was five to eighteen weeks. In our experiments in which only testicular fragments were present, or in which a testicular castration was made, the time of latency was in general fourteen days, only in two animals three to four weeks.

(6) There is no possibility that our results were caused incidentally by an especially favorable age of the males or females used in the experiments. We have shown that the advanced age of the male into which an ovarian graft is made, and the youth of the female from which the ovary is taken, do not influence much the result of the experiment. We succeeded in causing a feminine hormonic effect, even with milk secretion, in fully grown males weighing up to 845 gm.; we succeeded in causing a feminine hormonic effect by engrafting ovaries of animals only seventeen days old. The time of latency was in all these experiments again only two weeks.

(7) The short time of latency was not caused by the fact that a special place (the kidney) was chosen for the ovarian

graft. We have succeeded in causing a hormonic effect in a male with a testicular fragment by engrafting the ovary in the abdominal cavity, the time of latency being again about two weeks, as in the intrarenal experiments.

(8)   The definite proof that the testicle can inhibit the hormonic effect of the ovarian graft is given by those experiments which may be best designated as *unbolting experiments:* (a) An animal having both testicles in situ and an ovary in the kidney showed as usual no feminine hormonic effect, whereas an animal with a testicular fragment and the second ovary of the same female revealed a feminine hormonic effect in less than two weeks. Now, seven weeks after the ovarian transplantation, both testicles were removed in the first animal, and eleven days later there was a striking hormonic effect. (b) Nine males with both testicles in situ were engrafted by the intrarenal method with one ovary each. There was no feminine hormonic effect three to eight weeks later. Now, from five animals both testicles were removed; four to ten days after testicular castration a feminine hormonic effect set in in four of these animals, whereas the uncastrated animals remained negative. This is really an *experimentum crucis* leaving no doubt as to the inhibiting influence of the testicle on the ovarian graft.

(9)   It is of the greatest interest that not only operative reduction of the testicular mass but also operative interference alone on the testicle is capable of "unbolting." This is shown by the following experiment. In three males resection of the cauda epididymidis was made, and an ovary was engrafted into the kidney; all three males revealed a feminine hormonic effect. The testicles were found fixed by adhesions in the abdominal cavity. The time of latency was from about two and a half weeks to two and a half months.

(10)   The unbolting effect can be obtained also by causing experimental cryptorchidism in a male engrafted with ovary, without resection of the epididymis. Five males were engrafted with ovaries by the intrarenal method and a few days later both testicles were fixed in the abdominal cavity to cause cryptorchidism. Three animals revealed a feminine hormonic effect. The time of latency was about three weeks.

After all these observations there can be no doubt that *the hormonic effect of the engrafted ovary depends also upon the quantity and the condition of the testicular mass simultaneously present.* There are cases in which the ovary survives and reveals follicular development, notwithstanding the presence of both testicles in situ, but there is then no feminine hormonic effect. *When discussing the "antagonism" between the sex glands it is absolutely necessary to discriminate between the survival of the graft and its hormonic effect.*

There are, however, at first sight some discrepancies. There was a feminine hormonic effect in the intratesticular experiments of Sand in about twenty per cent of the cases, notwithstanding the presence of both testicles. There were sometimes positive cases even when Krause engrafted by the intratesticular method only an ovarian fragment, both testicles remaining in the body. On the other hand, the intrarenal experiments which gave about one hundred per cent positive cases in animals with testicular fragments were always negative when both testicles remained in situ. How is this contradiction to be explained? Sand is of the opinion that the position of an intratesticular ovarian fragment is as to nutrition different from that of an ovarian fragment engrafted wherever it may be. But according to our experiments the explanation is quite another one. There is no doubt that the twenty per cent of positive cases in the intratesticular experiments with both tesicles in the body were caused by operative interference on the testicle of the engrafted animal; in most of the positive intratesticular experiments of Sand and of Krause one or both testicles were involuntarily fixed by adhesions in the abdominal cavity; the condition was quite the same as in our intrarenal experiments with experimental cryptorchidism (see paragraph 10). That the abnormal position of the testicle is the unbolting factor is shown also by another set of experiments.

(11) In four male animals engrafted with one ovary each, a bilateral resection of the epididymis or a bilateral ligature of the vas deferens was made *by the scrotal route* so as to exclude experimental cryptorchidism. There was no feminine hormonic effect during six to eight weeks of observation. Removal of the testicles was then performed in two of the animals with resec-

tion, and in one the feminine hormonic effect set in four days later.

(12) In the same way as the feminine hormonic effect of the ovary is inhibited by the testicles in situ, *the masculine hormonic effect of a testicular fragment can be inhibited by an ovarian graft,* though this is not always necessarily the case. In experiments with Voss we found twice, in males with ovarian grafts and a positive feminine hormonic effect, the presence of testicular fragments with ripe spermatozoa, whereas the male sex stigmata were characteristic for a castrated animal. I *never* saw a similar coincidence in numerous cases of partial castration in guinea pigs in which testicular fragments *alone* were present.

At the moment it is not possible to give a definite explanation of the mechanism underlying the inhibitory influence which the testicle in situ has on the hormonic effect of the ovarian graft. It is not probable that the hormone production of the ovary is always inhibited in these cases, since it has been shown by different authors that the ovarian graft which does not exhibit an hormonic effect can reveal follicular development. This is shown also by our statement that in the unbolting experiment (see paragraphs 8 and 11) the feminine hormonic effect began within a *few days* after the removal of the testicles from the engrafted animal. There was even a case in which the feminine hormonic effect set in in less than two days after unbolting. The same is shown also by the following observation.

(13) We examined *simultaneously* the condition of the ovaries of the *same* female in an animal with both testicles in situ in which there was no feminine hormonic effect, and in an animal which revealed a feminine hormonic effect a few days after unbolting. *The ovaries were quite identical in both animals.*

Our experiments in which the displacement of the testicles to the abdominal cavity were "unbolting" factors make it highly probable that some processes going on in the seminiferous tubules are in play in the inhibiting action of the testicle. But the question is a quite difficult and delicate one, as shown by the following two statements.

(14)   In an engrafted animal with bilateral resection of the epididymis in which there was for eight weeks no feminine hormonic effect, the testicles were removed and four days later a feminine effect set in (see paragraph 11). Microscopical observation revealed that in both testicles the seminal tubules were highly reduced. In this case the testicles were able to perform their antagonistic influence though the seminal tubules revealed no signs of spermatogenesis.

(15)   The mechanism underlying the unbolting effect of experimental cryptorchidism seems to be quite a special one. This is shown by the following two sets of experiments.   (a) Twenty-one unilaterally castrated male guinea-pigs were intrarenally engrafted with ovaries; there was a feminine hormonic effect in five cases, but the time of latency was of five to seven *months*.   (b) In thirteen male guinea-pigs a unilateral cryptorchidism was caused, the second testicle remaining intact in situ. The animals were intrarenally engrafted with ovaries. A feminine hormonic effect set in in three cases already about six *weeks* after the operation. It is clear that the presence of a retained testicle, besides the normal one, is a factor which favors the feminine hormonic effect. It is very likely that substances originating in the degenerating seminal tubules are here in play influencing the somatic substratum which becomes more able to react to ovarian hormones notwithstanding the presence of the second intact testicle.

Our experiments as yet lead to no definite conclusion of the question whether the antagonistic influence of the testicles in situ on the ovarian graft or on the hormonic effect of the latter and *vice versa* is a sex-specific one, caused by sexual hormones.

(16)   Finally another set of experiments may be mentioned which showed that the hormonic effect of an ovarian graft depends not upon resorption of hormones already present in the ovary at the time when the graft is made, but upon hormones produced in the surviving graft. There was never a feminine hormonic effect in those experiments in which rabbits' ovaries were engrafted into the kidney of male guinea pigs, the ovarian grafts not taking and undergoing degeneration.

Our experiments, which number more than one hundred and fifty, show that the problem of the antagonistic influence

between the sex glands is by no means negatively settled as Moore has claimed.

BIBLIOGRAPHY

1. Moore: Science (Utica), 1924, 59, 41.
2. Lipschütz & Krause: Compt. rend Soc. de biol. (Par.), 1923, 89, 220; 1135.
   Krause: Deutsche med. Wchnschr., 1923, 49, 1330.
   Lipschütz, Krause & Voss: J. Physiol. (Lond.), 1924, 58, 461. 1141; 1239; 1332; 1410; 91, 868.
   Lipschütz & Voss: Compt. rend. Soc. de biol. (Par.), 1924, 90, 1139;
   Lipschütz: Klin. Wchnschr., 1924, 3, 1903.
   Lipschütz: Rassegna di Studi Sessuali (Roma), 1924, 4, 297.
   Lipschütz: Compt. rend. Soc. de biol. (Par.), 1924, 91, 865, 870.
   Lipschütz: J. Physiol. (Lond.), 1924, 59, 333.

STUDIES ON THE PATHOLOGY OF THE HYPOPHYSIS
V. ABSCESS OF THE HYPOPHYSIS

J. P. SIMONDS

From the Department of Pathology, Northwestern University
Medical School

CHICAGO

Abscesses found in hypophyses removed at necropsy are usually only incidents in the course of a fatal acute infection occurring in some adjacent or distant part of the body. Such lesions thus discovered do not, *per se,* possess much practical clinical significance. Any clinical manifestations attributable to the suppurative process in the hypophysis either would not have time to display themselves, or they would be overshadowed and obscured by the more marked symptoms of the disease which was the immediate cause of death. However, from a study of such cases something may be learned of the etiology, pathogenesis and most common location of this lesion. Inasmuch as not all acute infections, such as are often found on postmortem examination to be complicated by abscess of the hypophysis, are fatal, a study of the conditions giving rise to this pathologic change may aid in the interpretation and explanation of some obscure cases of hypopituitarism. For this reason it has been thought that the following review of the literature and a report of seven new cases might be of some value and therefore warranted.

The first recorded case of abscess of the hypophysis appears to be that reported by Heslop in 1848 (1). Glinski (2) has reported a case of suppuration of the hypophysis in a 40 year old woman who died of pyemia two weeks after childbirth. Schmorl (3) mentioned abscess of the hypophysis as an accompaniment of "embolic processes associated with sepsis." M. Simmonds (4), in a paper on embolism of the hypophysis, reported four cases of abscess, and made the startling statement that "in the anterior lobe bacterial emboli may remain without effect or they may cause anemic infarcts, while in the posterior lobe they lead to the formation of abscesses." Plant (5) has

taken exception to the first part of this statement, and reported nine cases of abscess of the hypophysis. In five cases the lesions were multiple, and all were located in the neurohypophysis. Four of his cases followed abortion with septic thrombosis; two were associated with osteomyelitis with thrombophlebitis; two complicated malignant endocarditis; and one occurred as part of a general septicemia. Schaefer (6) reported metastatic abscesses in all three lobes of the hypophysis in a soldier who died of streptococcus septicemia following a gunshot wound of the knee. He also described a perihypophyseal abscess in a case of generalized staphylococcus infection.

Cases of acute suppurative hypophysitis complicating purulent sphenoidal sinusitis have been reported by Harvey (7), Meyer (8), and Boggs and Winternitz (9). Glinski (2), Smoler (10), Thom (11) and Plaut (5) have reported abscesses in the anterior lobe of the hypophysis as an accompaniment of purulent leptomeningitis.

In my series of over two hundred hypophyses examined in serial sections, seven instances of abscess have been found. Six of these were in the anterior lobe, and one in the posterior lobe. A brief summary of these cases follows:

Case 1. White male, about 65 years old. Death was due to subdural hemorrhage possibly resulting from trauma. The hypophysis was about one and one-half times the normal size. Within the capsule in the median plane of the anterior surface was an abscess large enough to occupy more than one low power field of the microscope. The interstitial tissue of the anterior lobe immediately beneath the abscess was infiltrated with polymorphonuclear leucocytes.

Case 2. Thirteen year old white boy. There were bilateral suppurative otitis media and mastoiditis complicated by purulent leptomeningitis. Beneath the capsule on the front of one lateral half of the anterior lobe of the hypophysis was an abscess about one-fourth the size of the entire lobe.

Case 3. Well nourished white male, 11 years old. Acute suppurative otitis media was complicated by purulent leptomeningitis. The hypophysis was about one and one-half times the normal size. Almost one entire lateral half of the anterior lobe had been destroyed by an abscess.

Case 4. Well nourished colored female, aged 39 years. Evidence of lobar pneumonia, acute fibrinous pleurisy, acute pneumococcus leptomeningitis, ulcerative aortic endocarditis and acute glomerulonephritis was observed. The hypophysis was very slightly enlarged. Immediately beneath the capsule of the hypophysis was a zone of infiltration with polymorphonuclear leucocytes extending around almost the entire periphery of the gland. From each side the infiltration dipped in between the anterior and posterior lobes, separating these structures and more or less completely destroying the middle lobe.

Case 5. Female, 33 years old. There were serofibrinous pericarditis, fibrinopurulent leptomeningitis, multiple abscesses of the brain, hypostatic bronchopneumonia, acute suppurative tracheobronchial and mediastinal lymphadenitis. The hypophysis was slightly enlarged. In the anterior part of the anterior lobe was an extensive subcapsular abscess involving about one-third of the anterior lobe, and situated chiefly lateral to the median plane.

Case 6. Poorly nourished white female, 46 years old. There were caseous tuberculosis of the right lung, chronic fibrous and acute fibrinopurulent pleurisy on the right side, unhealed thoracostomy wound, purulent leptomeningitis and ependymitis, and multiple small abscesses of the brain. The hypophysis was about normal size. Just beneath the capsule at one antero-lateral border was a small, roughly triangular abscess, about the size of one low power field of the microscope. Surrounding the abscess on two sides was a zone of hyperemia in which the interstitial tissue was infiltrated with polymorphonuclear leucocytes.

Case 7. White male, aged 26 years. Examination showed ulcerative mitral and mural endocarditis, multiple anemic infarcts of the kidneys and spleen, and multiple small septic infarcts of the brain. In one antero-lateral quadrant of the posterior lobe of the hypophysis was a small abscess about the size of one low power field of the microscope.

The etiology of the abscess in the capsule in Case 1 is not clear. No clinical history was obtainable, and the circumstances under which the necropsy was done made a satisfactory examination of the associated pathological conditions next to impossible. The remaining six cases illustrate the two distinct ways in which abscess of the hypophysis may originate, namely, by the lodgement of mycotic or septic emboli, and by extension from a suppurative inflammation of nearby structures.

Case 7 was definitely, and Cases 5 and 6 probably, of embolic origin. In the two last mentioned cases purulent leptomeningitis was present, but each showed also multiple "metastatic abscesses" in the brain. In Case 6 the abscess was wedge-shaped and, therefore, had the form of an infarct. Furthermore, in each instance, the purulent infiltration of the capsule was less marked than in the other cases with meningitis. It is at least possible, therefore, that septic emboli may give rise to abscesses in the anterior, as well as in the posterior, lobe. Case 6 is especially interesting in this connection. There were no vegetations on the heart valves. It is well recognized that bronchiectasis and other inflammatory conditions of the lungs may be complicated by multiple abscesses of the brain. This case suggests the possibility that these diseases may also give rise to abscess of the hypophysis. It is this group of embolic abscesses that is of special interest to the endocrinologist. For these

patients have at least a chance of recovery, and may later show otherwise unexplainable evidences of deficiency of function of the pituitary.

The group of hypophyseal abscesses complicating purulent leptomeningitis (Cases 2, 3 and 4) is interesting chiefly because of the mechanism by which the infection reaches this gland. These abscesses are most commonly situated immediately beneath the capsule in one of the antero-lateral quadrants of the anterior lobe. In a later paper it is hoped to present some observations on the blood supply of the hypophysis. Suffice it to state here that two fairly large arteries enter the front of the anterior lobe, one on either side, and at a little distance from the sagittal plane. These vessels penetrate the glandular portion of the hypophysis and pass to the rich plexus of vessels in the core of connective tissue which is located at about the center of each lateral half of the anterior lobe. The infection appears to enter the hypophysis along one or the other of these blood vessels, perhaps by way of the perivascular lymphatics. In this connection, the case of Boggs and Winternitz (9) is of special interest because the primary focus of infection was in the sphenoidal sinus and probably reached the hypophysis, without involving any other structures, by the route just mentioned. In Case 4, the abscess was located between the anterior and posterior lobes. The infection probably gained access to the hypophysis along blood vessels which Benda (12) has described as entering the lateral surface and passing medialward between the neurohypophysis and the glandular portion.

<div align="center">SUMMARY</div>

1. Seven new cases of abscess of the hypophysis are reported and the mechanisms by which the infection reaches this gland are described.

2. Abscess of the hypophysis may be embolic in origin and may involve either the anterior or posterior lobes or both. It may occur as a complication of acute endocarditis, pyemia, or bronchiectasis and chronic inflammatory processes in the lungs and pleura. Such diseases are not invariably fatal, and patients recovering from them may later show evidences of hypopituitarism.

3. Abscess of the hypophysis is a not very infrequent complication of purulent leptomeningitis. The lesion in these cases is usually located just beneath the capsule in one antero-lateral quadrant of the anterior lobe. The infection appears to enter the gland along the perivascular lymphatics of one or both of two blood vessels which enter the anterior surface of the anterior lobe lateral to the median plane. Or it may enter along blood' vessels which penetrate the lateral surface, and the abscess then develops between the anterior and posterior lobes.

BIBLIOGRAPHY

1. Heslop, T. P.: A case of hypertrophy with abscess of the pituitary body. Dublin Quart. J. M., 1848, 6, 466.
2. Glinski, L. K.: Anatomische Veraenderungen der Hypophyse. Przegl. lek. (Kraków), 1913, No. 1; abst. in Deutsche med. Wchnschr. (Leipz. & Berl.), 1913, 39, 473.
3. Schmorl: Discussion on the pathology of the hypophysis. Verhandl. d. deutsch. path. Gesellsch. (Jena), 1914, 17, 231.
4. Simmonds, M.: Ueber embolische Prozesse in der Hypophyse. Arch. f. path. Anat. [etc.] (Berl.), 1914, 217, 226.
5. Plaut, A.: Hypophysenbefunde bei akuten Infektionskrankheiten. Arch. f. path. Anat. [etc.] (Berl.), 1922, 237, 165.
6. Schaefer, H.: Beitrag zur Lehre von den Entzuendungen spezifischer und nicht spezifischer Natur in der Hypophyse. Diss., Path. Inst. (Jena), 1919.
7. Harvey, J. R.: Sudden and complete amaurosis; scrofulous tumor compressing the optic nerves; abscess of the pituitary gland; caries of the body of the sphenoid bone. Dublin Quart. J. M., 1855, 20, 220.
8. Meyer, O.: Demonstration einiger seltener Praeparate von Hirntumoren und Erkrankungen der Hypophysengegend. Ztschr. f. Psychiat. (Berl.), 1918, 74, 521.
9. Boggs, T. R., & Winternitz, M. C.: Acute suppurative hypophysitis as a complication of purulent sphenoidal sinusitis. Johns Hopkins Hosp. Rep. (Balt.), 1919, 18, 56.
10. Smoler, F.: Ueber ein operierten Fall von zystischen Hypophysen tumor. Prag. med. Wchnschr., 1914, 39, 71.
11. Thom, W.: Untersuchungen ueber die normale und pathologische Hypophysis cerebri des Menschen. Arch. mikr. Anat. u. Entwckl. (Bonn), 1901, 57, 632.
12. Benda, C.: Pathologie der Hypophysis cerebri. Flatau-Jakobson's Handb. d. path. Anat. d. Nervensystems (Berl.), 1904, p. 1429.

CASE REPORT OF A PSEUDOHERMAPHRODITE

G. L. ROHDENBURG, M.D.
From the Pathological Laboratory, Lenox Hill Hospital
·NEW YORK CITY

Instances of malformation of the genital organs of such degree as to bring into question the sex of the afflicted individual are still sufficiently uncommon to warrant the report of instances as they may be encountered. The present case is that of a child aged 20 months, who, 22 hours before death, was admitted to the hospital in coma. The parents stated that the genital abnormality was recognized at birth and that after deliberation the physician in attendance decided that the individual was a boy. Aside from the genital condition there were no stigmata of endocrine defect in evidence.

Post-mortem examination revealed the cause of death to be chronic interstitial nephritis with small granular kidneys of the type usually seen in those dying in advanced age. Histological examination of the kidneys showed advanced glomerular fibrosis, marked increase in the kidney stroma, and vascular sclerosis approaching obliteration of the vessels. Accompanying this was cardiac hypertrophy, the left ventricle wall measuring 1.6 cm. in diameter.

Inspection of the genital organs showed what appeared to be a penis 3 cm. in length, covered by a foreskin which could be retracted. Situated 0.5 cm. below the root of the penis was an opening 0.6 cm. in diameter from which urine was said to have escaped. This opening pouted and on the lower wall, 0.3 cm. from the cutaneous edge, was an opening through which a probe could be passed into the vagina. Embracing but not concealing the penis were two labia having the characteristics of the labia majora; the labia minora were absent.

Lying behind the bladder was the vagina, 3.6 cm. in length, which, except for a minute opening, ended blindly against the urethral wall. Into the vagina there projected a uterus, 4.2 cm. in length, which was completely divided by a septum from cervix to fundus. There was no definite tubal formation, the

uterine horns being prolonged so as to form tubes; these prolongations were 4 cm. in length. One cm. from the distal end of the left tube was an ovoid pearly white body 1 cm. in length,

Figure 1   C, clitoris or penis; u, urethra; b, bladder; v, vagina; h, opening of vagina into urethra; I and II, body of uterus with septa; s, testes; III, muscular wall of uterus; IV, masculine genital remnants

and on the opposite tube at the same location there was a thickening of the wall.

Histological examination of the vagina showed the epithelial lining to be normal. The uterine body and tubal extensions

Figure 2   Photomicrograph; X 250. Embryonic testis attached to uterine horn

were lined by stratified squamous epithelium and were devoid of glandular structure. The thickening of the right tubal wall

was shown to be due to an island of tissue, apparently the vas deferens, adjacent to which was a small canal lined by columnar epithelium (spermatic cord?). The ovoid body attached to the left tubal extension was an embryonal testis, the histological features of which are shown in the accompanying photomicrograph. There were no abnormalities of any of the other endocrine glands.

SUMMARY

The case is reported of an individual with the external genitals resembling the male and the female and with internal genital organs consisting of a bicornate uterus with a septum, and one gonad, an embryonal testis, a portion of the vas deferens and a spermatic cord.

THE EFFECT OF FEEDING FOWLS ON THYROID GLAND

BORIS ZAVADOVSKY

Biological Laboratory of Sverdlov University
MOSCOW

Although the literature contains many reports of thyroid treatment in numerous species of animals, the only work found on thyroid feeding in fowls is that of C. J. and C. Parhon.[*] These investigators observed as a result of thyroid treatment marked excitability, tremors and complete ischemia of the comb. Increased resistance to fowl cholera was also reported.

The observations herein reported were begun in the summer of 1919 at the Zoological Gardens of New Ascania in South Russia, under the guidance of Prof. Michael Zavadovsky. The work was continued during 1919 and 1920 in the laboratory of Prof. B. P. Babkin at Odessa. From the fall of 1920 on, the work has been continued at our own laboratory at Moscow. During this period over sixty fowls have been experimented upon, not including controls.

METHOD OF INVESTIGATION

The method of the experiments consisted in feeding the fowls on thyroid gland. The glands were taken from domestic animals and obtained directly from the slaughter house; in Ascania Nova they were from sheep, in Odessa from cattle, and in Moscow from horses mostly. Poehl's desiccated tablets and Parke-Davis preparations were also used. Most recently lumps of desiccated gland prepared in the winter of 1923 from thin slices of horse glands in a thermostat at a temperature of 50° to 60° celcius were employed.

It was only last August (1923) that by the kindness of Dr. Sandberg of Chicago a small quantity of thyroxin was obtained. Its action proved to be identical with that of the fresh glands. However, circumstances do not permit a detailed consideration of these experiments with thyroxin and a closer analy-

*Parhon, C. J., & Parhon, C.: Note sur l'hyperthyroïdisation chez les oiseaux et sur la résistance des animaux ainsi traités aux infections spontanées. Compt. rend. Soc. de biol. (Par.), 1914, 76, 662.

sis of the results of the experiments until the next report.   In this paper the effect of thyroid gland on the fowl's organism from various points of view will be dealt with.

The doses at first were large enough to produce rapid results of acute and even fatal poisoning, varying from one to twelve sheep glands or from one to one and a half beef or horse glands.

Figure 1.   The cock of bred "Minor" in the state of moulting.

As controls part of the fowls during the first experiments were given an equal or even larger amount of meat.   But it has now been demonstrated beyond all doubt that the symptoms described are attributable specifically to the action of the thyroid, and not to meat in general.   Such control experiments no longer seem necessary.   As occasion arises all further variation and changes in the method employed will be duly noted.

Experimental moulting. The accelerated moulting that within a short time all but strips a bird bare is one of the most striking and evident symptoms of hyperthyroidism. Three or four days after the commencement of the treatment are sufficient to weaken the roots of the feathers so that they fall out easily every time the bird is handled. In eight to ten days the feathers begin to fall out of themselves. The moulting is the more pronounced, the larger the doses, and can be so severe that the whole yard is strewn with feathers, and the bird goes about entirely naked. The intensity and rapidity with which moulting sets in varies slightly with the quantity of gland administered, but, generally speaking, it begins within eight to ten days.

The growth of white feathers. The very first experiments showed that under the influence of thyroid feeding completely black fowls produced in place of the moulted black feathers a new plumage with an abundance of white feathers. This was true not only of the wing feathers which are generally very susceptible to blanching even in thoroughbreds but to the body feathers also, converting the pure black fowls to a greater or lesser degree to spotted. In a second series of experiments an identical result was obtained in black fowls having at the beginning not a trace of white on them. This whitening regularly takes place in all instances in twenty-five to twenty-seven days after the first administration.

Acute poisoning. In all the experiments already described mostly very large doses of thyroid gland, approximately three to six sheeps' gland a day, were given. A quantity exceeding six glands was enough to cause marked depression. The cock would sit with ruffled feathers on one spot, or stroll listlessly about the yard, his wings hanging slightly down. While in this state the bird moulted very actively. In such cases unless the thyroid feeding was discontinued or if the dose was increased to ten to twelve glands, curious convulsive fits that terminated in death were observed. The phenomena of poisoning have been so similar in my experiments that the description of one instance will be sufficient.

Experiment No. 6. Langshan cock, halfbred white, age four to five months. The experiment began on July 13, 1919. Thyroid glands —four to eight daily—were administered for a period of eight days, amounting to fifty-two glands in all. On July 21 a plentiful moult

was in progress. The next day twelve glands were administered; on the next, ten. On July 24 several interesting changes in behavior were noted; it had previously been very shy, but had now become quite tame. Two thyroid glands were offered to it, of which it ate only one, pecking off the mark and with no assuredness. One hour later it was found lying exhausted in the middle of the yard. When lifted, after a few steps taken with difficulty, it fell down again. It would not peck at any grains. One hour later it was observed again lying in the same position on its side, with its legs stretched out. During the next two hours it had several attacks of convulsions at intervals of five to ten minutes. Death then ensued.

The foregoing experiment might be regarded as inconclusive, there being a possibility that the color changes observed were not attributable to the thyroid feeding, but were merely incident to growth, as often happens with fowls. A further study was therefore carried out, upon thoroughbred black fowls.

A pure black cock was kept in a state bordering on poisoning from beef thyroid glands (obtained from the slaughter house) over four months, except for a few intermissions when it was fed with milk, wheat bread and the like. Within three months (December 11, 1919, to March 9, 1920) it was made at will to moult completely, each time developing a larger plumage of white feathers and a very decided thinning of the black pigment in what remained.

In accordance with the instant at which a given plumage was obtained it was possible to secure on a general background of scanty black feathers a new plumage sometimes pure white, sometimes black tipped with white, a condition abnormal in fowls.

The following abridged protocol will give some idea of the course of the experiment.

Experiment No. 12 at Odessa. On Dec. 11, 1919, two Langshan cocks and three hens five to six months old were purchased. They had not yet moulted. The cock only was fed thyroid, the others being provisionally kept as control birds.

From Dec. 11 to 16, inclusive, the cock was given nine beef glands, i. e. one and a half a day. On Dec. 17 a depressed condition was observed. The dosage was then cut down to one-sixth to one-eighth of a gland. On July 18 the cock remained motionless, incapable of eating or drinking unaided. Food placed in the throat was swallowed greedily. When its beak was thrust into a cup of water it drank eagerly. Towards the end of the meal it tried to drink for itself but missed the basin when it bent its head. It then tried to peck but did not even touch the floor. The feathers were dropping in huge quantities, bestrewing the whole floor. It had lost much flesh; the crop was empty. On Dec. 20 the condition was much the same, though the cock was livelier and sometimes pecked successfully. On Dec. 24, 1921, the condition was improved: as before, no gland was administered. It now pecked vigorously but at the observer's

trousers, fingers, etc., and anything else except the grain held out in the hand. It often pecked ridiculously at the air, missing the food which was some little distance away. The feathers continued to fall in heaps.

On Dec. 25 the cock had lost nearly all its feathers. Otherwise it had recovered completely save for its eyesight. It was again given half a gland, and this provoked a condition of severe illness. The administration of thyroid gland was discontinued until Dec. 31.

Dec. 29, systematic measurements were begun on the cock and on the control hen. The cock, which was at first larger than the hen, now weighed 1650 gm. against 1810 gm. for the hen. From Dec. 31 to May 1 the cock was given one-sixth to one-fourth of a gland daily and it increased in weight. The control hen began to moult normally.

On Jan. 6, 1921, young white feathers were noticed for the first time on the breast and tail among many black stumps. But the new growth was slow and the quills were crumpled. The dose was raised to half a gland daily.

By Jan. 7 a large number of white feathers had appeared on various parts of the body. From Jan. 8 to 17 a quarter to a third of a gland was daily administered, with occasional interruptions. During this period the bird was again slightly ill. The young black feathers that had begun growing densely on the back and elsewhere gradually turned purplish-grey.

The appearance suggested that the production of pigment had entirely ceased and the old stock of pigment was being distributed over a larger surface in proportion to the growth of the plumage. Some feathers were purplish-black at the tip, but pure white everywhere else. But the growth of the new plumage was still very slow; new white feathers made their appearance in fresh places, and some old ones still grew, but long feathers on the wings and tail did not grow at all.

Jan. 18, the lassitude and ataxia previously described had reappeared. Jan. 19, it would not eat at all. Artificial feeding was resumed. The weight had fallen to 1500 gm. Jan. 18-26, the treatment was interrupted and the cock was fed bread and milk.

During this period of intermission of treatment the plumage grew very much more rapidly, the wing feathers beginning to grow partly white and partly black with large white spots near the tips; whereas during the second period of gland treatment the roots of the young feathers that had started after the first period of the treatment had weakened and were beginning to drop.

Jan. 27, the third period of treatment began. The cock regularly received a twelfth, eighth or quarter of a gland. Feb. 6, it had half a gland, and the next day the symptoms of derangement of gait and incoordination reappeared so that it had to be artificially fed.

Many new white feathers were appearing on the wings. Feb. 8, 10 and 11, it had doses of a twelfth of a gland and appeared better, eating with a good appetite. From Feb. 18-27 it was given in increased doses up to a third or a half of a gland. The most evident effect was excitability, restlessness, muscular tremors, thirst, very loose bowels and much flatulence.

Feb. 28, the cock was again utterly depressed, the feathers moulted considerably, and the weight had decreased noticeably. From this point the thyroid treatment was suspended and the cock recovered and again was pecking, though only from the palm, not from the floor. The feathers continued to drop as at every period of treatment.

March 4, the cock showed a general dark coloring with occasional white feathers. Most of the white plumage was concealed beneath the wings and colored parts. At the same time many other peculiar-

ities were observed; postponed growth and development, an outward appearance which might be called either senile or infantile; a pale comb, half grown; stunted growth; absence of spurs; and bent and knotted legs.

After reaching such a condition the cock recovered a normal condition, but with surprising tardiness. On March 21 there was a great increase in size, and the comb turned red, only at this stage acquiring the characteristic backward fold on to the forehead and sharp dentation. However, the cock still startled and amazed onlookers with its imbecility, strutting about crazily and stumbling over the other fowls and rabbits in the pen. The roosting instinct was absent and it never even tried to crow.

April 28, for the first time it displayed something like a sexual instinct. On May 12, when approaching the hand with the grains in it, it uttered for the first time the cock's characteristic note, the cluck that summons the hens; but it still could not peck one grain at a time, and had to be fed by hand. After this date exact observations could not be continued, but in June the cock began crowing and pairing.

Autopsy, July 20, showed the following conditions. The comb and gills had grown almost to normal size and become a bright scarlet, and the bird had grown strong and increased in weight (2480 gm.). The plumage had become duller than is usual in this variety in spite of very many contour feathers which had grown afresh after the conclusion of the experiment and covered up the white feathers. The tail feathers were just beginning to grow, but very much delayed. The characteristic of the legs remained unchanged.

The limits of space will not permit detail of other observations, but similar experiments left it beyond all doubt what were the specific and essential symptoms. Results such as those illustrated in Figure 1 prove that the different varieties of black fowls are subject to depigmentation (Langshan, Spanish and "Minors").

One point yet remained to be decided: was it only the black pigment that was liable to discoloration under thyroid feeding, or other colors as well? Incidental experiments with other varieties, mainly brown, yellow and grey, tended to indicate that the black was not in this respect an exception among other color pigments. It was decided to settle this question by experimenting on red plumed Rhode Island birds. The details of an experiment on such a bird corroborated our expectations.

Experiment No. 33 was carried out with the assistance of S. A. Azimova-Milietzcoja on a Rhode Island Red hen obtained with its sister and a cock from the great Moscow breeding station of Gorjunov.

Feb. 20-22, 1923, one-quarter horse thyroid gland daily was administered. Feb. 23-26, another quarter gland daily was given. Feb. 26, the hen, when handled, lost many feathers which remained in the observer's hands and easily fell out of their sockets. On

Feb. 28 both the experimental hen and the control had the feathers plucked off the right side of their legs to hasten pigmentary reaction. Feb. 29 to March 3, the treatment was interrupted. The hen moulted heavily, leaving its back absolutely bare; feathers dropped off the entire body. On the back and on the right side of the plucked leg white feathers grew, while red feathers grew on the control hen.

On March 8 a third of a gland was given, and on March 10, 12, 13 and 15 a quarter of a gland. After March 15 the experiment was discontinued, as the discoloration was most pronounced. The control hen, however, did not show a single white spot on the leg or any other part of the body. Figure 2 shows clearly the degree of whiteness attained by the hen under treatment, as compared with the control sister. The stuffed specimens were prepared July 13, 1923.

Figure 2.   The depigmented Rhode Island hen and her control sister.

Many similar experiments on various fowls, yellow, cream, grey Plymouth Rock (although mostly hybrids), confirm the view that *every pigmentation in fowls is subject to discoloration under thyroid gland treatment,* and apparently this process is faster in colors other than black. However, this latter supposition has not yet been conclusively proved.

To sum up the outcome of these lengthly observations two points may be taken as absolutely demonstrated: that treatment with thyroid gland will provoke premature moulting in fowls, capable of repetition with subsequent growth of white feathers, and a general change in the quantity of the pigment of the new plumage.

But these conclusions also involve a series of new problems bearing on the character of the effect of thyroid gland treatment.

At Ascania and Odessa the experiments were carried out on fowls between July and December, i. e. when fowls normally moult. Also, the doses used up to that time were very large, and beyond doubt exceeded the limits of normal physiological action of the thyroid gland. Therefore two questions remained to be solved. (1) *Would small (physiological) doses of thyroid gland produce analogous results on the moulting and the pigment?* (2) In the experiments reported the natural glands of sheep or oxen mostly were used. With the artificial prepara-

Figure 3. 1-9—Feathers of Langshan cock after thyroid feeding.
10-11—Feathers of control Langshan.
Middle row—Feathers of Rhode Island Red cock.
I and II before, and III-X after, the thyroid feeding.
A and F—Normal feathers of Rhode Island Red hen.
B-E—Depigmented feathers of a hen fed with thyroid.

tions of Poehl such exact and positive results in moulting and discoloration were not obtained and it was thought that these artificial preparations of the gland lacked this specific reaction. In this event, the theory would be confirmed that the hormone of the thyroid gland is not a simple body, but a complex of independent entities. Is such actually the case? *Do derived preparations yield the same result as natural glands?*

From Jan. 26 to Feb. 3 a mongrel black Spanish pullet, weighing 1217 gm., received about 10 gm. of Poehl's thyroidin either in tablets or in powder. In about one month from the beginning of the experiment the head was checkered with white, and soon after white spots also appeared on the wings and thighs. It is remarkable that the dose fixed upon for this experiment failed to produce a state of depression on this fowl; on the contrary, the weight increased to 1420 gm. There was no moulting at first; it began only after prolonged dosage, Feb. 10. This intense moulting lasted about ten days.

In view of this positive result the fowl from Dec. 14 onward was given natural horse gland, and as much as a quarter to a half gland a day. Towards the end of January she had such an abundance of white feathers that from raven-black she had turned into something like a speckled partridge.

The other hen was a cross with a few white and grey feathers on a background of black, of the same age, and weighing 1175 gm. She received the same doses and produced a plentiful white plumage, the white feathers amounting to two or three times the original number. The development in this case proceeded quite similarly to that of the other, both in the production of white feathers and in the commencement of the moulting.

Thus it was evident that the effective substance was present in the Poehl preparation. And further, these results were attained with doses of gland scarcely exceeding the physiological limits. The experiment affected both chickens toward the end of the normal moulting and therefore retarded the production of pigment in the normal growth of the young feathers. It appears that the young plumage is less liable to moulting than the old plumage. This conclusion was borne out by three further experiments which proved that *soon after the normal moulting the plumage is much more firmly attached and only very slightly subject to moulting,* even if very large doses of thyroid gland are administered.

The reversal of the depigmentation. One of the hens that showed a marked depigmentation was kept all the summer after the termination of the experiment in March, 1922. *In the*

autumn after the normal moulting she reassumed her black plumage.

On Dec. 1, 1922, she was again fed on horse gland, an eighth to a half of the gland daily. The feeding was continued until Jan. 12, 1923, with an interval from Dec. 7-22. Moulting began on Dec. 12. On Jan. 13 she died in typical convulsions, but abundantly covered with white feathers.

Neuropathological symptoms. In several other cases than that described in the first protocol special attention was paid to

Figure 4. Spanish hen after a second thyroid feeding.

the neurological effects of thyroid feeding. An outstanding result is general stupidity. Disturbed balance and lack of coordination in the nervous system as a whole is evident. Various aspects of the neurological problem remain for further study. In general the greatest development of neurological symptoms coincided with depression of weight and ischemia and shrinkage of the comb.

Control experiments. As previously stated, during the earlier experiments a considerable number of fowls were fed as controls with large amounts of meat concurrently with the fowls under thyroid treatment. In no case were symptoms observed anything like those seen in hyperthyroidized fowls. This fact raised the question: Does the depigmentation play an independent part in the symptoms as observed or is it merely a change due to the precedent moulting, a sign of a certain weakening of epidermal functions? To answer this, both control fowls and those undergoing treatment were frequently plucked on definite parts of the body, generally the thigh and under the wing. In every case the feathers of the control fowls when they grew afresh were of normal color, while the thyroidized fowls grew great patches of white feathers. It appeared also that the pigment reaction can be obtained with less thyroid than the moulting reaction.

Although already in possession of a whole series of control facts it was thought advisable to check the experiments in yet another way, by using fowls fed on other organs of internal secretion. Adrenal bodies were selected as most readily available and also because there is evidence that they have a direct functional (synergistic) relation to the thyroid gland.

Further, there is the well known fact of the bronzing of the skin in Addison's disease, which is connected with the affection of the cortex of the suprarenals. A posteriori, it might be supposed that if we introduced into the system doses of suprarenal glands far above the normal in quantity we might induce depigmentation of the dermis. The extent to which the suprarenal gland can evoke symptoms similar to those resulting from hyperthyroidism of fowls was therefore investigated. Thus, with the assistance of S. A. Miliezcoja-Azimova suprarenal in doses of one-fourth to a whole gland was administered.

Four fowls, two white and two black, and several controls were used. Suffice to say that with the exception of one case in which gain in weight was less than expected, no effect of the feeding as detected. The experiment was continued by the injection of adrenalin chloride (Parke, Davis & Co.) in doses from 2 to 10 cc. over a period of ten days. No effects were produced that could be related to the specific thyroid action.

\

SUMMARY AND CONCLUSIONS

1. Thyroid preparations were administered to about sixty fowls. These included dried or fresh glands of sheep, oxen and horses and Poehl's thyroidin. No significant differences in the effects of these preparations were observed.

2. The toxic threshold in birds proved to be much higher than in mammals.

3. The dosages ranged from minimal to fatal.

4. The symptoms of hyperthyroidism demonstrated were increased excitability, polyphagia, polydipsia and nervous disturbances which varied with the doses.

5. The neuropathologic disturbances included incoordination, convulsions and general stupidity.

6. An effect specific to fowls was observed in the plumage. Larger doses caused a marked loss of feathers. These were replaced by others which were completely colorless or white in varying degrees, depending upon dosage.

7. It is concluded that the thyroid gland plays a specific role in the regulation of the growth and moulting of feathers and in their pigmentation.

INCIDENCE OF GOITER AMONG SCHOOL CHILDREN.

DAVID C. HALL, M.D., CASSIUS M. HOFRICHTER, M.D., and GEORGE J. MOHR, M.D.

SEATTLE, WASHINGTON

Simple goiter, or benign enlargement of the thyroid gland, is of common occurrence in the United States. It is endemic in the entire basin of the Great Lakes and in the Pacific Northwest. King County, Wash., is in a region with large incidence of endemic goiter. The common occurrence of this condition locally will be testified to by any practicing physician, and the layman on the street can readily diagnose cases in abundance as he passes. Over fourteen thousand observations on local University students show an incidence of over twenty-six per cent, while an even more frequent occurrence of thyroid enlargement was noted in an investigation in a few of the public schools. Although decreased incidence of goiter in adults as contrasted with that noted in early life may be established, nevertheless the goiter in the adult, which often develops into the severly toxic type, may have its origin in the simple endemic goiter of childhood.

The endemiology and etiology of simple goiter have long engaged the attention of investigators. Various theories are proposed in this connection. The chemical hypothesis attributes the disturbance to the presence of various chemical agents in the water, such as magnesium, iron salts, calcium salts and iodine. The organic theory postulates the presence of toxin of organic nature in water. McCarrison's well known bacterial theory of the origin of goiter is supported by much evidence. The presence of acute or chronic infection, tonsillar, gastrointestinal, or of other focal origin, is at times considered responsible.

Whatever final conclusions may be arrived at relative to the ultimate cause of goiter, certain indisputable facts as to the control of its occurrence are now at hand. Kimball points out that iodine was used in a treatment of goiter by the ancient Greeks in the form of the ash of burnt sea sponges. Marine and

Lenhart show that in the dog, if a fragment of the thyroid gland no larger than one-sixth of the total normal tissue is allowed to remain in situ, and five-sixths of the gland removed, the fragment will not enlarge if the animal is given sufficient iodine to keep the fragment saturated. If the iodine content of the thyroid gland of animals is deficient in iodine, the young are born with goiters.

The active principle of the thyroid gland was isolated in crystalline form by Kendall in 1916. This substance is a stable compound of iodine. It loses its physiological activity, however, if the iodine is replaced by other halogens. The conclusion is then drawn that iodine is necessary for normal thyroid function. When there is a deficiency of iodine, the thyroid gland enlarges in an endeavor to meet the bodily demands for its normal secretion. Marine and Lenhart state that the iodine content of thyroid gland substance varies inversely with the degree of hyperplasia of the gland.

"Simple goiter is the easiest known disease to prevent" (Marine). This sweeping statement is fully substantiated by the experience of live stock owners in eradicating the disease from stock, and by the clinical results already obtained in various parts of the United States and in Switzerland. The accomplishment of prophylactic treatment of simple goiter centers around the work of Marine and Kimball, carried on in the city of Akron, Ohio. These workers obtained the permission of the School Board of Akron to work in the public schools, and outlined a method of approach which would give them clear cut and definite observations upon which to draw definite conclusions.

One man was chosen to do all the physical examinations, so that the observations might be consistent, and certain criteria were outlined which were arbitrary, but served as a guide to aid in classification. These criteria were as follows:

A thyroid gland was considered normal:

(a) Which was not visible, as a bulging across the trachea;

(b) Which had a barely detectable band of thyroid tissue across the trachea, on palpation;

(c) In which there was absence of a well-defined thyro-glossal stalk (so called pyramidal process).

Enlarged thyroids were grouped in three classes:

1. (a) Visible bulging of the skin over the thyroid isthmus;
   (b) A widened or thickened isthmial band or mass on palpation. (If the isthmus cannot be seen or felt it can be felt by having the child swallow while the finger or thumb is held against the trachea just below the cricoid cartilage.)
2. Moderate enlargement consisting of:
   (a) Gross deformity;
   (b) Bulging of the neck from the enlarged lobe;
   (c) Marked bulging of the skin anterior to the enlarged isthmus.
3. Marked enlargement consisting of those cases with excessive deformity.

The results obtained by these men, in brief, were as follows:

Of 2090 pupils taking iodine, 5 developed enlargement of the thyroid gland;

Of 2305 not taking iodine, 495 developed thyroid enlargement;

In 1182 pupils with enlargement of the thyroid gland at first examination, who took iodine, 773 thyroids were decreased in size;

In 1048 pupils with enlarged thyroid glands at first examination, who did not take iodine, only 145 decreased in size.

The experience of these men indicates that goiter is found six times as frequently in girls as it is in boys, and that the best ages for prophylactic treatment are from 11 to 17 years of age. A more recent survey in Grand Rapids, Michigan, covering over twenty-six thousand school children, does not bear out this ratio if thyroid enlargements of minor degree are included. The slight enlargements are much more common in boys than earlier statistics indicate, but have apparently been largely overlooked. This last observation is borne out in the King County District, herewith reported.

In 1918 goiter prevention by means of iodine administration was undertaken in Switzerland. At that time in one of

the Zurich schools one hundred per cent of the children were goiterous. A few milligrams of iodine was given weekly throughout the school year, with a resultant marked reduction in the incidence of goiter. In the Canton of St. Gall, in January, 1918, an incidence of 87.6% was reduced to one of 13.1% in January, 1922. On the basis of these results, prophylactic treatment of goiter is being extended throughout Switzerland.

With the above facts in mind, a committee appointed by the King County Medical Society, and composed of the signers of

FINDINGS OF 3160 EXAMINATIONS FOR GOITER
AMONG GRADE SCHOOL CHILDREN
(1506 GIRLS AND 1654 BOYS)

this report, undertook a survey of the school children of King County to determine accurately the incidence of goiter. One school was chosen, and after having studied carefully the criteria of classification as outlined by Marine and Kimball, the members of this committee spent some time in satisfying themselves that each man had a clear understanding of the interpretation

of the facts in hand. It did not take long to realize that there were many children in whom the isthmus of the thyroid gland was readily palpated and was from ¾ to 2 centimeters in breadth. In addition to this there was another group of children in whom the thyroid enlargement was so prominent that one could see bulging of the neck, and it was palpated so readily that it could easily be demonstrated to the teacher. The first group the committee decided to classify simply as palpable glands, while the second group was designated as definite enlargement of one, two or three degrees. Some three thousand children were examined according to these standards, and the results were submitted for investigation.

Pupils examined.....................	3,160
Boys examined	1,654
Girls examined.....................	1,506
Boys with goiter 1 and 2.............	588
Girls with goiter 1 and 2.............	655
Per cent among boys................	35.5
Per cent among girls................	43.4
Total percentage among boys and girls	39.3

TABLE 1

Age	No.	NOT PALPABLE		PALPABLE		NO. 1		NO. 2 AND 3		TOTAL GOITER	
		Neg.	%	No.	%	No.	%	No.	%	No.	%
6	319	150	47 00	75	23 8	90	28 2	3	0.94	93	29.14
7	325	117	36 00	102	31.38	104	32 00	2	0.6	106	32.6
8	395	157	39.74·	92	23.29	138	34 93	8	2.02	146	36.95
9	420	158	37 62	108	25 71	147	35 00	7	1 66	154	36.66
10	406	148	36 45	94	23 15	158	38 91	6	1.48	164	40.39
11	385	135	35 06	96	24 93	144	37 4	10	2.59	154	39.99
12	344	126	36 62	69	20 05	136	39 53	13	3.77	149	43.30
13	313	93	29.71	61	19.48	137	43 77	22	7.02	159	50.79
14	175	52	29 70	40	22 85	68	38 85	15	8 57	83	47.42
15	78	30	38 46	13	16 66	30	38 46	5	6.41	35	44.87
TOTAL	3160	1166	36 9	751	23.76	1152	36 45	91	2.88	1243	39.3

Findings of 3,160 Examinations for Goiter Among Grade School Children.

The findings presented in the chart indicate much earlier age incidence of goiter among school children than has hereto-

fore been noted. The relative incidence among boys as contrasted with girls is likewise much greater than earlier reported. This corresponds with the findings in Michigan. An apparent

TABLE 2

Age	No	THYROID NOT PALPABLE		THYROID PALPABLE		GOITER NO. 1		GOITER NO. 2 AND 3		TOTAL GOITER	
		No.	%	No.	%	No.	%	No.	%	No.	%
6	153	67	43 8	40	26 1	46	30 0	....	......	46	30.0
7	163	63	38 88	45	27 7	53	32.7	1	0.61	54	33.31
8	212	87	41 0	49	23.1	72	33 9	4	1.88	76	35.78
9	216	79	36 57	61	28 23	73	33 79	3	1 38	76	35.17
10	235	100	43 45	52	22.7	82	34 9	1	0 42	83	35 32
11	191	77	40 31	47	24 6	63	32 98	4	2 09	67	35.07
12	180	86	47 7	35	19.4	56	31 6	3	1 66	59	33 26
13	170	56	32 9	37	21 71	71	41.76	6	3 52	77	45 28
14	87	35	40 23	21	24.13	26	29 88	5	5 74	31	35.62
15	48	23	47 91	6	12 50	18	.37 15	1	2.08	19	39 58
TOTAL	1654	673	40 6	393	23 7	560	33 85	28	1 69	588	35 5

Findings of 1,654 Examinations for Goiter Among Grade School Boys.

TABLE 3

Age	No.	THYROID NOT PALPABLE		THYROID PALPABLE		GOITER NO. 1		GOITER NO. 2 AND 3		TOTAL GOITER	
		No.	%	No.	%	No.	%	No.	%	No.	%
6	166	83	50 00	36	21 68	44	26 5	3	1.8	47	28 3
7	163	54	33 12	57	34 97	51	31 29	1	0 61	52	31.9
8	183	70	38 24	43	23 49	66	36 06	4	2.19	70	38 25
9	204	79	38 72	47	23 03	74	36 27	4	1.96	78	38.23
10	171	48	28 07	42	24 56	76	44.44	5	2 92	81	47.36
11	194	58	29 89	49	25 26	81	41 75	6	3.09	87	44.84
12	164	40	24 39	34	20 73	80	48 78	10	6.09	90	54 87
13	143	37	25 87	24	16 78	66	46 15	16	11.19	82	57.34
14	88	17	19 31	19	21 59	42	47 95	10	11 3	52	59 25
15	30	7	23 33	7	23 33	12	40 0	4	13 33	16	53 33
TOTAL	1506	493	32 7	358	23 7	592	39 3	63	4.1	655	43 4

Findings of 1,506 Examinations for Goiter Among Grade School Girls.

drop in the percentage of enlarged thyroid glands at the age of 14 in boys, and 15 in girls, is not so reliable as the findings plot-

ted up to those ages, since relatively few examinations of children 14 and 15 years of age were made.

BIBLIOGRAPHY

1. Guilder, Ruth P.: Incidence of goiter among college students. Ann. Clin. Med. (Balt.), 1923, 1, 248.
2. Reed, T., & Clay, H. T.: A survey of thyroid enlargement among the school children of Grand Rapids. J. Mich. M. Soc. (Grand Rapids), 1923, 22, 323.
3. Watt, C. H.: Simple goiter—its local prevalence. J. Med. Ass. Georgia (Augusta), 1923, 12, 177.
4. Pearce, N. O.: Incidence and prevention of thyroid disease among children. J. Lancet, 1923, 43, 157.
5. Hall, D. C.: Prevalence of goiter in the Northwest. Northwest Med. (Seattle), 6, 189.
6. Hall, D. C.: Prevalence and distribution of goiter in Washington. Ibid., 371.
7. Schlesinger, E.: Ztschr. f. Kinderh. (Berl.), 1920, 27, 207; abst., J. Am. M. Ass. (Chicago), 1921, 76, 1376.
8. Kraeuter, J.: München. med. Wchnschr., 1922, 69, 47; abst., J. Am. M. Ass. (Chicago), 1922, 78, No. 4.
9. Skolstad, S.: Norsk Mag. f. Laegevidensk. (Christiania), 1921, 82, 729; abst., J. Am. M. Ass. (Chicago), 1921, 77, 1613.

THE EFFECT OF PITUITARY PREPARATIONS ON THE NITROGEN METABOLISM*

G. P. GRABFIELD AND A. M. PRENTISS
BOSTON, MASSACHUSETTS

The influence of the glands of internal secretion on metabolism is so firmly established that we were led, in the course of another investigation, to administer various pituitary preparations to patients on a constant protein intake to see if any effect on the nitrogenous output could be demonstrated from preparations which have been shown to .exert a profound influence on growth and water metabolism.

Various attacks have been made upon this problem, but the results have been conflicting (1, 2). In these experiments human subjects were used. With three exceptions all were physically normal adults. Of these three, two were Mongolian idiots and one was a cretin, but these also were of adult calendar age. These three patients were studied at an earlier period and blood determinations were not carried out. The methods used were those of Folin (3) for both blood and urine except for the uric acid determinations which were done by Benedict's method (4). Complete nitrogen partition was determined daily on the urine. The patients studied were kept in a small ward and their activity was limited to walking about the ward. All the food served to them was cooked in a small diet kitchen on the ward and carefully weighed by a nurse especially trained for this work.†

The drugs used were commercial extracts bought in the open market. The doses were as follows: "Pituitrin (Surgical)" 1.0 cc., "Posterior Pituitary" 20 mgms, "Anterior Pituitary" 324 mgs., "Whole Pituitary" 324 mgms. These doses were given three times a day after meals. The results are

shown in the accompanying tables. Table 1 shows the effect of anterior and posterior lobe administration to normal subjects. The blood figures show no constant change in any of the nitrogenous constituents, though earlier studies (5) with the methods then available seemed to show an increase in the blood uric acid after administration of desiccated pituitary. Similarly no constant change can be demonstrated in the nitrogen metabolism as shown in the output of urinary nitrogen.

The experiments with Pituitrin and whole gland (Tables 2 and 3) likewise show no demonstrable effects on the nitrogen metabolism in these experiments. It is to be especially noted that no significant variation in the nitrogen partition occurred in either blood or urine.

SUMMARY

No effect on the urinary nitrogen excretion or non-protein nitrogen of the blood was observed in these experiments as a result of the administration of either pituitrin (intramuscularly), dried anterior lobe, dried posterior lobe or dried whole gland pituitary (by mouth) to patients on a constant diet.

BIBLIOGRAPHY

1. Malcolm, J.: J. Physiol. (Lond.), 1903, 30, 270.
2. Schafer, E. A.: Quart. J. Exper. Physiol. (Lond.), 1912, 5, 203.
3. Folin, O.: A laboratory manual of biological chemistry. D. Appleton & Co., N. Y., 1922.
4. Benedict, S. R.: J. Biol. Chem. (Balt.), 1922, 51, 187.
5. Hammett, F. S., Patten, C. A., & Suitsu, J. N.: Am. J. Physiol. (Balt.), 1920, 51, 588.

(Tables will be found on following pages.—Publishers.)

TABLE 1

Table 1. Experiments showing the effect of surgical pituitrin (1 cc. t. i. d. intramuscularly) on blood and urinary nitrogen. The drug was administered on the first three days of the experiment, so that the anaylses of days Nos. 2, 3 and 4 show the effects during the exhibition of the drug. The first day is free from any drug influence, being the last day of a control period.

TABLE 1

Subject	Day of experiment	URINE						BLOOD					
		Total nitrogen	Urea nitrogen	Ammonia nitrogen	Uric acid	Creatinine	Rest nitrogen	Non-protein nitrogen	Urea nitrogen	Amino acid nitrogen	Creatinine	Uric acid	Rest nitrogen
C VIII	1	6 0	4.5	.4	.3	1 3	.4	27 3	15.2	6 8	1.4	4.5	3 3
	2	5 0	3 9	.4	3	1.1	.3	25 6	14 3	6 7	1.3	3 8	3 9
	3	5 1	3 9	4	.3	1.4	.3	29 1	13 1	6 0	1 3	4 2	8 2
	4	6 2	5 0	4	.3	1 5	2	33 1	18 8	7 4	1 2	3 6	5 3
	5	6 5	5 3	.4	.3	1 3	2						
	6	5 0	4 0	3	3	1 3	.1						
W XI	1	7 3	5.4	5	4	1 5	.8	25 8	10 8	5 4	1.4	4.1	7.8
	2	5 7	4 3	3	.3	1 6	.4	27 2	12 6	6 0	1 2	3.4	7.1
	3	6 9	5 5	3	3	1 5	.5	24 5	12 3	5 4	1 2	3 7	5 1
	4	7 7	6 3	4	3	1 7	2	26 3	15 0	6 4	1 3	4 6	2 9
	5	7 6	6 4	.4	.3	1.4	.2						
	6	6 8	5 1	4	.3	1 5	7						
P XIII	1	8 5	6 6	7	4	1 5	6	25 0	13 1	5 9	1 4	3 5	4 3
	2	7 7	5 8	4	3	1 1	1 0	24 5	13 0	5 7	1 4	3 4	4 1
	3	7.7	5 5	6	3	1 1	1 0	23 4	14 1	5 9	1 3	3 3	1 9
	4	8 1	6 3	7	4	1 5	5	26 9	12 5	5 7	1 1	3 4	7 2
	5	7 2	5 9	.5	3	1 3	3						
	6	8 7	6 3	.5	3	1.2	1 3						
Ha 21 (Mongolian idiot)	1	4 5	3 4	4	3	.9	3						
	2	5 7	3 5	4	3	1 1	1 7						
	3	4 8	3 4	4	4	1 2	.5						
	4	4 0	3 0	3	3	8	3						
	5	4 6	3 4	4	4	1 1	3						
	6	5 5	4 0	3	4	1 2	7						
Da 21 (Cretin)	1	4 √	2 8	3	4	8	6						
	2	4 0	1 5	2	3	7	2 0						
	3	3 0	2 5	3	3	7	8						
	4	2 5	1 8	2	2	6	2						
	5	3 2	2 7	2	3	7							
	6	4 0	2 5	3	3	7	9						
Sp 21	1	7 6	5 6	4	5	1 7	8						
	2	8 0	3 7	5	5	1 8	3 0						
	3	7 5	5 5	5	4	1 6	9						
	4	7 7	5 8	5	4	1 8	1 0						
	5	7 1	5 8	4	4	1 2	4						
	6	7 8	5 1	5	5	1 9	1 4						

TABLE 2

Subject	Day of experiment	URINE						BLOOD						Drug
		Total nitrogen	Urea nitrogen	Ammonia nitrogen	Uric acid	Creatinine	Rest nitrogen	Non-protein'l nitrogen	Urea nitrogen	Amino acid nitrogen	Creatinine	Uric acid	Rest nitrogen	
G IX	1	4.8	3.4	.4	.4	1.1	.1	25.0	7.7	5.8	1.3	3.2	9.9	
	2	4.7	3.1	1.0	.3	1.1	.1	26.0	6.3	5.4	1.2	3.7	11.7	Anterior pituitary 1.0 gram t.i.d.p.c.
	3	4.2	2.7	.5	.4	1.1	.5	25.2	8.0	5.2	1.2	3.2	10.4	
	4	3.8	2.7	.5	.3	1.0	.1	26.1	8.6	4.9	1.1	2.8	11 3	
	5	5.1	3.3	.9	.4	1.0	.3							
	6	4 5	2.8	.4	.4	1.1	.8							
P X	1	6 3	4.5	.5	.3	1.4	.7	26.1	6.2	5.2	1.3	3.5	13.1	
	2	5.7	4.1	.9	.3	1.3	.1	25.0	7.0	4.9	1.3	3.7	11.4	Anterior pituitary 1.0 gram t.i.d.p.c.
	3	6.7	5.2	.4	.3	1.4	.5	21.4	8 0	4.7	1.1	3.8	7.0	
	4	4 3	3.3	.3	.2	1.4	.1	24 2	5.5	4.8	1.1	3.6	12.3	
	5	9.2	5.9	2.1	.4	1.9	.3							
	6	6.3	4.4	.3	.3	1.3	1.0							
J XII	1	8.0	5 2	.4	.4	1.8	1.6	25.4	5.7	6.0	1.5	4.1	11.8	
	2	7.0	4.8	.3	.4	1.6	1.2	25.4	6.3	5.2	1.3	4.2	12.0	Anterior pituitary 1.0 gram t.i.d.p.c.
	3	7.3	5 4	.7	.4	1.4	.5	25.2	7.1	5.1	1.3	4.0	11.2	
	4	5.6	4.1	.5	.3	1.3	.4	25.9	8.6	5.4	1.2	3.6	10.3	
	5	8 1	5.7	.6	.5	1.8	.9							
	6	5 9	4.3	.7	.3	1.5	.3							
P X	1	6.4	4.9	.2	.3	1.2	.6	23.1	10.1	5.1	1.1	4.2	6.1	
	2	6 1	5.2	.2	.3	1.1	.2	20.1	9.9	5.2	1.1	3.7	3.4	Posterior pituitary 20 mgms. t.i.d.p.c.
	3	4.1	2 9	.1	.3	.9	.7	21.5	11.0	5.1	1.2	3.6	3.4	
	4	5 7	4 5	.3	.3	1.3	.3	20.9	11.0	5 7	1.3	4.4	7.2	
	5	4 6	3 5	.1	.2	.8	.6							
	6	8 3	6 0	1.1	.3	1.6	.5							
J XII	1	6 2	4.4	4	.3	1.4	.8	23.1	8.5	8.8	1.1	3.3	4.3	
	2	5.2	3 9	2	.3	.9	.6	21 5	9.9	5.4	1.2	3.7	4.6	Posterior pituitary 20 mgms. t.i.d.p.c.
	3	4 1	2 7	3	.3	1 3	.5	26.8	9.4	5.9	1.3	3.9	9.7	
	4	2 2	1 8	.1	.1	.5	.1	22 1	10 6	5.1	1.2	3.2	4 9	
	5	7 6	6 0	.5	.3	1 7	.4							
	6	7 6	5 5	5	3	1.4	1.0							

Shows experiments with anterior and posterior lobe administration. Arrangement as in Table 1.

TABLE 3

Subject	Day of experiment	Total nitrogen	Urea nitrogen	Ammonia nitrogen	Uric Acid	Creatinine	Rest nitrogen
Da 21 Cretin	1	3 2	2 0	2	.3	.7	7
	2	2 8	2 1	.2	.2	6	.1
	3	8	6	1	2	.2	...
	4	4 1	2.8	3	4	8	.6
Sp 21 Psychoneurosis	1	8 6	6 2	4	.5	1 8	1.2
	2	8 1	6 0	1 0	5	1 8	.3
	3	8 6	6 7	4	6	1 7	.7
	4	7 6	5 6	4	5	1 7	9
Ha 21 Mongolian	1	5 7	4 7	.3	5	1 1	.2
	2	5.2	3 6	5	4	1 1	.4
	3	3 8	2 8	4	4	8	.2
	4	5 7	3 4	4	3	.9	1 5
Ca 21 Mongolian	1	6 1	4 4	2	5	1 2	9
	2	5 9	4 7	2	4	1.2	5
	3	5 2	3 9	3	4	1 0	5
	4	6 6	5 1	.3	.5	1 0	.8

Table 3 shows effect on urinary nitrogen output of whole desiccated pituitary (1 gm. t. i. d. p. c.) administered for two days. The second and third days of each experiment correspond to the exhibition of the drug.

Book Reviews

THE INTERNAL SECRETION OF THE SEX GLANDS. Alexander Lip-
schütz, 1924. Williams & Wilkins Co., Balt. Pp. 513.

Professor Lipschütz has given us in his new book one of
the most comprehensive discussion of the endocrine function of
the sex glands that has yet appeared. The general theme of the
work as stated in the opening chapter is this: to what extent is
it possible to show that the ontogenetic development of the
sexual characters is influenced by the sexual glands, and that
the further persistence of these characters depends on the pres-
ence of the sexual glands? In formulating his answer to this
question he considers in turn the evidence that has accumulated
from experiments on castration, on the transplantation of
ovaries and testes, and on the feeding of sexual glands or the
injection of their extracts. In each case a concise statement of
the results obtained by the more important investigators in the
field is first given, followed by an able consideration of the the-
oretical significance of these results. By this line of reasoning
Lipschütz proves the existence of the testicular and ovarian
hormones. He then turns his attention to the consideration of
the parts of the sex glands concerned in the elaboration of these
hormones. After a careful weighing of the available evidence
the conclusion reached in regard to the testes is that in the
mammal "the interstitial cells are a necessary part of the endo-
crine apparatus," while "no proof exists of a direct hormonic
action by the cells of Sertoli or by the other constituents of the
walls of the tubules independently of the interstitial cells." The
author is inclined, however, to believe that while the generative
cells are not concerned directly in the elaboration of a hormone,
still the process of spermatogenesis or some stage in the process
is connected with the transformation of the interstitial cells into
an active endocrine apparatus. In the case of the ovary the
author concludes that it is highly probable that in the mammal
the internal secretion is elaborated partly by the membrana
granulosa, and partly by the cells of the theca interna, and that
these cells originate from follicles undergoing atresia or from
ripe follicles rupturing and transforming themselves into cor-
pora lutea.

There is a chapter on the isolation of the sexual hormones
and another in which the author shows that there is little or no

evidence to support the view that the prostate, seminal vesicle, or genital passages are concerned in the elaboration of a hormone although it is probable that the secretions of these parts of the genital apparatus are of great importance to the vitality of the spermatozoa. This is followed by an interesting discussion of the various types of hermaphroditism, eunuchoidism and sexual precocity. The chapter on the sexual hormones and morphogenesis should be of especial interest to geneticists, for in it Lipschütz discusses at some length the problem of sex determination and even succeeds, to a certain extent, in harmonizing his theory of the indifferent character of the soma with the existence of sex chromosomes. The final chapter deals with the problem of rejuvenation and in it the author attempts to show to what extent our knowledge of the sexual hormones may be of importance in the practice of medicine.

The book should have a wide appeal, as it contains material of almost universal interest. All biologists and medical men will find a wealth of valuable material in it, while even the layman without biological training will find much of the book interesting and understandable.—F. A. Hitchcock.

LES SYNDROMES HYPOPHYSAIRES ET EPIPHYSAIRES EN CLINIQUE INFANTILE. Pierre Lereboullet, 1924. J. B. Baillière et Fils, Paris. Pp. 135.

The writer reviews the literature on the experimental physio-pathology of the hypophysis and epiphysis and correlates the findings with the syndromes and morphological changes presented in clinical cases of infantilism. The relation of the hypophysis to osseous dystrophies, glycosuria, polyuria, diabetes insipidus and the adiposogenital syndrome, in young persons, is discussed, together with treatments. The monograph also includes a report of the relation of the epiphysis to precocious puberty, and a discussion of treatments (organotherapy, radiotherapy, and surgery).—M. O. Lee.

PREPARATION OF SCIENTIFIC AND TECHNICAL PAPERS. S. F. Trelease & Emma S. Yule, 1925. Williams & Wilkins Co., Balt. Pp. 113.

The editorial policy of this journal is to restrict this department to review of publications pertaining technically to endocrinology. The excellence and timeliness as well as the need for this little book by Trelease and Yule, however, seem to justify a departure from custom. It is a book that could profitably be read by the great majority of contributors to current scientific literature. It has been evolved, not from the authors' inner conscious-

ness, but from years of experience in which it has been placed as a guide in the hands of technical students. The reviewer upon first reading the book began to mark special passages for comment, but so many admirable things were encountered that the attempt was given up. The outstanding features are a clear, concise presentation of the methods of effective organization of material, a discussion of points of usage frequently overlooked, and an enlightening description of the technic of transforming a manuscript into a printed article. The book is as readable as it is informing.—R. G. H.

Abstract Department

The effect of administering adrenal cortex to young guinea pigs
(Primi risultati di ricerche sperimentali sugli effetti della som-
ministrazione di corticale surrenale sull' accrescimento somatico
di giovani cavie). Castaldi (L.), Rendic. d. R. Accad. d. Lincei,
1924, 33 (I Sem.), 94-96.

The addition to the ordinary diet of young guinea pigs of 3 to
10 c. per kilo of a dry extract of cortex of suprarenal glands causes
a considerable increase in their somatic development. In comparison
to untreated controls the animals are heavier and fatter and their
skeleton is bigger; the hair reaches an unusual length, particularly
in females. If the same extract is administered to pregnant animals
the young are larger than those of controls. The administration of
the extract prolonged for months does not give rise to toxic or
anaphylactic phenomena.—Physiol. Abst., 9, 543.

The effect of double adrenalectomy on the development of rickets
in rats. Hess (A. F.) & Jaffe (H. L.), Proc. Soc. Exper. Biol.
& Med. (N. Y.), 1924, 22, 103.

On a defective diet controls and completely adrenalectomized
rats developed rickets to the same degree and at the same time.
The authors concluded, therefore, that the functional activity of
the adrenals is not an essential or an important factor in the patho-
genesis or cure of rickets.—J. C. D.

Measurements on the cortical cells of the human adrenal (Messungen
an der Zellen der menschlichen Nebennierenrinde). Kolliner
(Martha), Ztscher. f. Anat. u. Entwcklngsgesch. (Berl.), 1924,
70, 321-335.

This report includes a tabulation of measurements on the size
of whole cells and nuclei and shows the relation of the two in 29
human subjects, from a 6 cm. fetus to 49 years of age, and in 2
apes. There is surprisingly little change from the fourth fetal
month to the adult stage. Literature is cited.—A. T. R.

The relation of adrenalin to the action of insulin upon the blood
sugar content. Mueller (E. F.), Lewi (M. J.) & Myers (C. N.),
Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 22, 142-146.

Nine rabbits were tested for their reaction to adrenalin and then for their reaction to insulin. These same rabbits were then injected with both substances.

It was concluded that adrenalin and insulin, administered to the same animal, do not eliminate their mutual actions. In some instances, adrenalin injections made simultaneously with the administration of insulin increase the action of insulin by lowering the blood sugar content more than usual. In some instances, the action of insulin is only slightly diminished in the first tests (2 hours after administration), while the findings after 4 hours manifest an increase in the insulin action, usually observed at that period. It has been demonstrated that (in more than 70% of the cases examined) the insulin effect is generally not eliminated by adrenalin, but is sometimes enlarged. The reasons for these findings have hitherto not been discovered. They may be based upon an action of the involuntary nervous system.—J. C. D.

Studies in Addison's disease. Rowntree (L. G.), J. Am. M. Ass. (Chicago), 1925, 84, 327-335.

From the analysis made by Rowntree of forty-seven cases of Addison's disease no new facts are definitely established, but, despite the lack of pathologic and bacteriologic evidence, it is impossible to exclude a casual relationship between influenza and Addison's disease, even though it may not be direct. The most accurate data in this study relates to the last twenty-one cases. Thirteen of the patients in this series are dead, the average duration of the disease being sixteen and one-half months. The shortest duration was six weeks, and the longest definite history three and one-half years. Asthenia and pigmentation were present in every case, though in varying degrees. These two symptoms and hypotension were utilized as criteria in making the diagnosis. Gastro-intestinal complaints of one kind or another were present in practically all cases. Anorexia, nausea and vomiting were common, and in all probability were directly responsible for the loss of weight. Of the other gastro-intestinal symptoms, constipation is common, but is often interrupted by marked diarrhea for two or three days. Belching and bloating are also present at times. Pain is not usually described as a symptom of Addison's disease, but a considerable number of patients complained of vague, dull, deep aching pain in the epigastrium, lumbar region or flanks. This may be unilateral or bilateral, and possibly may be suprarenal in origin. Dyspnea, collapse and syncope are probably related to the feeble cardiac action and to the low blood pressure. Shock, or a condition closely

resembling it, has been observed in several cases. The patient is usually conscious, has a low temperature and an extremely low blood pressure, and the flesh feels cold to touch. There may be blood concentration, as evidenced by decreased water content in the blood, and increased difficulty in obtaining venous blood. The blood sugar of one patient, during the shock period, was 0.045 per cent. The pulse rate was between 70 and 100, and weak and compressible, but regular. The heart action was feeble usually, and the apex beat difficult to locate. On auscultation, the sounds were uniformly distant and feeble, and could be heard somewhat better with the ear than with the stethoscope. The respirations were extremely interesting in some cases, especially during the shock-like periods. In one case, they were markedly decreased, nine each minute, irregular in character and interrupted by frequent sighs. Interesting tracings were obtained in two cases. In one, a pneumographic tracing was taken and proved to be similar or identical to the tracing of Biot and to those published later by Conner. The tracing on the second case was somewhat similar, but not identical. So far as Rowntree is aware, these are the only instances recorded of this type of breathing in cases other than those in which there is meningitis or other intracranial lesions. In both cases, moderate acidosis was present. The first patient has improved markedly under treatment. The second responded slightly at first, but nausea and vomiting with extreme hypotension and asthenia continued until death. No suggestion of meningitis existed in either case. The laboratory studies may be summarized briefly. The urine was approximately normal and consistently sugar free. Water tests indicated poor excretion. The fasting blood sugar determined on admission was below normal in nine cases. Gastric contents were studied in nine of the twenty-one cases. In five of these, achlorhydria was present. The total and free acids were low in every instance. Roentgen-ray examination of the chest disclosed evidences of tuberculosis in four cases. Basal metabolism tests were carried out in thirteen cases, eight falling within normal limits. In this group of cases, anemia was infrequent, although a cardinal symptom according to Addison. Differential counts were made in fourteen cases, nine showing a definite lymphocytosis, reaching 50 per cent or more in four cases. The polymorphonuclear cells were decreased proportionately. In two cases tested, hepatic function was undisturbed. Necropsies were obtained in eight cases, and the pathologic involvement of the suprarenals and kidneys was confirmed at operation in another instance. It is rather significant that of the nine cases coming to necropsy, tuberculous lesions were found in eight; in the other case, the process was one of high grade

atrophy. The treatment employed by Rowntree was the so-called Muirhead regimen. The principle of the treatment is the frequent administration of epinephrin hypodermically and by rectum, and of whole gland or suprarenal cortex by mouth to the point of tolerance. This involves the determination of tolerance, which varies widely in each individual case. Once established, it becomes an index to dosage, although the tolerance of the same patient may also vary somewhat from time to time. Other therapeutic factors, such as rest, exercise, diet, outdoor life and sunshine, merit consideration. During the advanced stage and especially during shock, rest in bed should be absolute, and artificial heat is indicated. In stronger patients, moderate exercise, fresh air and sunshine are desirable. Because of the low level of the blood sugar, the diet should be rich in carbohydrates, with feedings at regular and frequent intervals. Long periods of fasting result in exacerbation of weakness; consequently, fruit juices and milk are advocated between meals, and during the night one serving of milk or fruit juice. A small dose of epinephrin is given by proctoclysis during the early morning hours to patients extremely ill. The results of treatment depend to a certain extent on the degree of tolerance which, inexplicably, varies greatly. Patients in the earlier stages, as a rule, tolerate large doses of epinephrin, from 5 to 10 minims (0.3 to 0.6 cc.) or even 15 minims (0.9 cc.), three times a day, hypodermically; from 5 to 10 minims rectally, and from 5 to 10 grains (0.3 to 0.65 gm.) of whole gland or cortex by mouth three times a day. Of the twelve patients on the Muirhead regimen, five are dead and seven living. Notable results were obtained in five instances. Three of these patients are living, are in excellent health, in view of the circumstances, and are continuing treatment after the lapse of from twenty to twenty-six months. The two other patients continue to improve after thirteen and nineteen months, respectively. Emphasis is placed by Rowntree on the improvement accruing under forced organotherapy. The results have exceeded expectations in several instances. On the other hand, despite most thoughtful and continuous efforts, five of the twelve patients died under treatment. The prognosis in Addison's disease is extremely grave. At best, the treatment can only combat functional insufficiency of the suprarenal glands. The treatment probably exerts no influence on the fundamental pathologic processes underlying the addisonian manifestations. Rowntree is of the opinion that since nothing better is available, the Muirhead treatment should be given a fair trial in every case of Addison's disease, care being exercised, however, to see that the patient's individual tolerance is determined and given due consideration, and that simul-

taneously every measure is utilized in combating the associated symptoms and the underlying pathologic process.—A. M. A.

The influence of compounds of known structure on the development of tadpoles (Fortgesetzte Studien über die Beeinflussung der Entwicklung von Kaulquappen durch Verbindungen mit bekannter Struktur). Abderhalden (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, 206, 467-472.

Growth and metamorphosis are influenced by a single dose of 0.0015 gm. 3-5-diiodotyrosine in 100 cc. water. Hydroxytryptophane accelerates tadpole metamorphosis in similar fashion to diiodotyrosine and thyroid. Iodized, this compound is more active. Insulin inhibits growth and metamorphosis, and in not too small doses is harmful, frequently producing edema and death.—A. T. C.

Insulin and adrenin action on animals on different diets (Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe. II, III. Insulin und Adrenalinwirkung bei verschiedenartig arnährten Tieren). Abderhalden (E.) & Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, 205, 547-558; 559-570.

Rats on a carbohydrate-free diet react less to insulin than rats on rich carbohydrate diet, but give with adrenin more marked hyperglycemia, though no increase in gas-exchange. Rabbits on acid diet (oats) react less to insulin than others on alkaline diet (green food), but give more marked hyperglycemia with adrenin; their alkali reserve is less than that of animals on green food.

—A. T. C.

Influence of diet on the action of certain internal secretions. IV (Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe). Abderhalden (E.) & Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, 206, 451-459.

Combined adrenin and insulin injection into rabbits shows the adrenin effect with animals on acid diet, and the insulin effect with animals on alkaline diet.—A. T. C.

Lipoids in the adrenals and gonads of rabbits (Lipoidbefunde in Nebennieren und Keimdrüsen beim Kaninchen). Bär (R.) & Jaffé (R.), Ztschr. f. Konstit. (Berl.), 1924, 10, 321-328.

In the adrenal cortex and in the gonads are found regularly phosphatides, cerebrosides and glycerinesters. Cholesterinesters and cholesterin-fatty acid mixtures are found only occasionally and then usually in small quantities. In the adrenals of castrated animals there is considerable fatty acid and soap, probably due to

degeneration of the adrenal cortex.   In 2 rabbits fed on cholesterin
the adrenals and ovaries contained large quantities of cholesterinesters but no phosphatides and cerebrosides.   This is regarded as
evidence that the lipoids are not secretion products but are merely
stored in the cells.—A. T. R.

**Absorption of sugar by the isolated heart in the different forms of
endocrine insufficiency.**   Kopelansky (D. S.).   Pub. from Lab.
Gen. Pathology, Univ. of Saratoff, 1925.

The work was done on the isolated hearts of dogs and cats.
The heart was nourished in Ringer-Locke solution with the addition of 0.125% of sugar.   Sugar determinations before and after
experimentation were made by Bertrand's method.   The data indicate that extirpation of the pancreas leads to diminution of absorption (almost 3 times less) of sugar by the isolated heart; the
same is true after parathyroid extirpation (almost 2 times less).
Extirpation of the thyroid gland, the thymus, and especially the
suprarenals, is accompanied by increased glucose absorptive power
of the heart.   On examination of combined insufficiency, an outstanding antagonism was observed between the pancreas group on
the one hand and the thyroid and suprarenal capsules on the other.
There appeared to be no effect from extirpation of testicles on exterior parathyroid.   Subcutaneous injection of adrenalin causes less
absorption of sugar by the heart.   If adrenalin is added to the
nutritive fluid (heart normal), the absorption is doubled.   When
insulin is added to the nutritive fluid (heart in normal state), the
absorption increases 3 times or more.   The absorption increases
also in the heart of an animal with adrenal diabetes if adrenalin
is added to the nutritive fluid.   The isolated heart of an animal
depancreatized but treated with insulin absorbs the glucose more
than in the normal state.—M. W. C.

Constitution and cardiac changes in inanition (Die Herzensänderungen beim Hungern im Zusammenhang mit seinem konditionellen Besonderheiten als eines Organs).   Stefko (W. H.), Ztschr.
f. Konstit. (Berl.), 1924, 9, 501-516.

It is concluded from a study of human material that cardiac
hypoplasia and atonia of the vascular and muscular systems are
apparently related to certain changes in the gonads and adrenals.
                                                          —A. T. R.

A case of dwarfism (Ein Fall von Zwergwuchs).   Wetzel (R.),
Ztschr. f. Konstit. (Berl.), 1924, 10, 211-228.

Physical and röntgenographic findings in a female dwarf 60
cm. high at 6 years of age.   With the possible exception of some

hypophyseal disturbance, the endocrine organs appeared to be normal, although they were not intensively studied. Literature is cited.—A. T. R.

Continuation of secretion of the ovarian follicular hormone by the human corpus luteum. Allen (E.) & Doisy (E. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 22, 303-305.

Studies with human material obtained at operation and tested on ovariectomized rats show that the follicular hormone is secreted after the formation of the corpora lutea. In swine and cattle the hormone has not been found in corpora lutea. The authors emphasize the fact that the follicular hormone acts on the vagina and uterus in the absence of the ovary and, therefore, influences these parts directly and not by way of the ovary.—J. C. D.

Influence of castration on motor nerve energy (Influence de la castration sur l'energie nerveuse motrice). Athanasiu (I.) & Pézard (A.), Compt. rend. Acad. d. sc. (Par.), 1924, 178, 874-876.

The action current of the gastrocnemius during voluntary walking is in capons only 20% of that in normal cocks. The nervous system is more influenced by castration than is the muscular system.—A. T. C.

Significance of the right rudimentary genital gland in the hen (Sur la signification de la glande génitale rudimentaire droite chez la Poule). Benoit (J.), Compt. rend. Acad. d. sc. (Par.), 1924, 178, 341-344.

Since ovariotomy in hens leads to development of a testis with complete spermatogenesis at the expense of the right rudimentary sexual gland (called at present the right rudimentary ovary), this should be considered as a rudimentary testis.—A. T. C.

Endocrine activity of the young testis in fowls (Sur l'activité endocrine du testicule impubère chez les Gallinacés). Benoit (J.), Compt. rend. Acad. d. sc. (Par.), 1924, 178, 881-883.

Testes in even the 20-day chick condition the growth of the comb —A. T. C.

A new case of experimental sexual inversion in the domestic fowl (Sur un nouveau cas d'inversion sexuelle expérimentale chez la poule domestique). Benoit (J.), Compt. rend. Acad. d. sc. (Par.), 1924, 178, 1640-1642.

Removal of ovaries caused development of sexual organs of male character, and of secondary sex characters.—A. T. C.

Stimulation of the surviving rabbit uterus by serum of pregnant and parturient women (Die Erregung des überlebenden Kaninchenuterus durch Schwangeren- und Kreisendenserum). Brdiczka (G.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1924, **103**, 188-195.

The serum of parturient women, also juice expressed from the placenta, produce strong contractions and a very definite increase in the tone of the isolated rabbit's uterus. The same effect is produced by serum from the blood of women in the 9th and 10th months of pregnancy; serum taken during the 6th and 7th months is relatively ineffective. Reasons are given for assuming that the activating substance is not adrenalin, but an as yet unidentified body formed in the placenta.—Med. Sc., **11**, 259.

Lipoid metabolism in the ovary with regard to the menstrual cycle together with investigations on the adrenals and mammary gland (Der Lipoidstoffwechsel der Ovarien mit besonderer Berücksichtigung des Menstruationszyklus nebst Untersuchungen an Nebennieren und Mamma). Berberich (J.) & Jaffé (R.), Ztschr. f. Konstit. (Berl.), 1924, **10**, 1-27.

A study based on material from women and cows. The largest amount of lipoid (cholesterinesters and cholesterin-fatty acid mixtures) in the corpus luteum of menstruation is reached when the granulsoa is at its highest, i. e., about 3-4 weeks after ovulation. Fatty acids and soaps are found only in atresia. Acute diseases have no influence. Amenorrhea due to chronic diseases may finally result in a total loss of ovarian lipoids. Cholesterin-fatty acid mixtures and cholesterinesters are regarded as merely storage products. The lipoid content of the adrenals is not related to the ovarian content. Literature is cited.—A. T. R.

Dental investigation in homosexual men (Gebissuntersuchungen an homosexuellen Männern). Dobkowsky (T.), Ztschr. f. Konstit. (Berl.), 1924, **10**, 191-210.

The study is based on over one hundred cases, each of which is tabulated as to general sexual habitus and dental and gingival characteristics. The average size of the teeth of homosexual men lies between the normal male and female dimensions. There are more dental irregularities and decay in homosexual than in normal men. While the cause of these degenerative changes in the teeth and gingiva have frequently been attributed to dysfunction of the endocrine organs, Dobkowsky believes that the dental changes are due to the same factors that are responsible for the general homosexual constitution. Undoubtedly there is some relationship between these anomalies and the generative organs. Literature is cited.—A. T. R.

Etiology of hermaphroditism and other anomalies related to sex (Entstehung krankhafter Zwittrigkeit und anderer Störungen der geschlechtlichen Beziehungen. Kritik der Inkretionstheorie). Greil (A.), Ztschr. f. Konstit. (Berl.), 1924, 10, 121-190.

An extensive and critical examination of the subject shows that many etiological factors other than endocrine may be responsible for these anomalies. These include developmental irregularities, infections, intoxications, trauma during intrauterine life, severe nutritional disturbances in the mother, psychopathic conditions, etc. Literature is cited.—A. T. R.

Morphology and experimental investigation (gonad transplantation) in aged dogs (Morphologische und experimentelle Untersuchungen an alternden Hunden). Harms (W.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1924, 71, 319-381.

The endocrine glands in general (thyroid, hypophysis, adrenals) showed evidences of hypofunction, and degeneration was usually present. The gonads showed the usual senile changes, the interstitial cells of the testis being well preserved. Transplantation of sex glands in several old animals was followed by evidences of rejuvenescence with evidences of regeneration in the gonads. Section of the vas deferens is not considered safe. Literature is cited.
—A. T. R.

A reaction of the testicular hormone (Sur une réaction de l'hormone testiculaire). Lagrange (E.), Compt. rend. Acad. d. sc. (Par.), 1924, 179, 923-924.

Successive injections of 0.1 to 0.2 of fresh rabbit's testis into adult female rabbits produce after some days atrophy and discoloration of the ovaries (which vary between 37 to 130 mg., instead of 125 to 800 mg.). Sterility sets in between 15 to 20 days, and lasts 6.5 months. The corpus luteum atrophies. If the female is impregnated previously, these results do not follow. The effects are transitory. They are not produced by testes from other species injected into rabbits.—A. T. C.

Onychauxis in a eunuchoid. Remarkable improvement following implantations of testicular substance. Lisser (H.), Arch. Dermat. & Syph. (Chicago), 1924, 10, 180-182.

This is the report of the case of a man of 31 whose testicles had atrophied as a result of an accident 11 years previously. When seen he had become eunuchoid, was mentally sluggish, and had physical inertia. The distribution of hair was feminine in type, and the nails showed onychauxis, that is, simple thickening. He

was still potent, and libido also was present to a fair degree. He had been treated with thyroid, anterior lobe of pituitary, and testicular extracts, singly and in combination, by mouth before being seen by Lisser. He had derived, according to his own statement, some slight and transient benefit from such treatment, but it had effected no improvement in the nails. A piece of fresh ram's testicle was implanted into the abdominal wall of the patient. This was followed by a gain of 5 lbs. in weight, marked increase in the size of the patient's testicular remains, and a subjective sense of well being and increased strength. He now was able to work fairly continuously for a year and a half, whereas previously he had been unable to hold a post for more than a week or two. The nails became somewhat smoother during this time. Twenty-one months later, after he had had a nervous breakdown, partly due to domestic troubles, a teaspoonful of semi-solid ram's testicular substance was forcibly injected subcutaneously into the abdominal wall. The patient gained 7 lbs. in the first week following this procedure. He gained strength and returned to work. Three more similar injections were given in the next 12 months. No unpleasant local or general reactions occurred, and the injected material was gradually absorbed between treatments. At the end of this time the finger nails had become entirely normal and the toe nails nearly so. No local treatment had been given to the nails. The article is illustrated with 3 photographs showing the nails before and after treatment. Two references to the literature are given.
—Med. Sc., **11**, 75.

Lipoids in the testes in general affections (Die Hoden bei Allgemeinerkrankungen). Lotz (A.) & Jaffé (R.), Ztschr. f. Konstit. (Berl.), 1924, **10**, 99–110.

A histological study of 55 pairs of fully developed human testes with special reference to the lipoid content. In general the amount of phosphatides and cerebrosides in the intratubular tissue is greater than the amount of cholesterinester and cholesterin compounds. In the interstitial cells the relative proportion of these two classes of compounds is reversed. In the aged the intratubular phosphatides and cerebrosides may entirely disappear. In diabetes mellitus there is a decrease in all the intratubular lipoids and in the phosphatides and cerebrosides in the intertubular tissue. There is no correlation between the testes and the adrenals with reference to the weight or lipoid content.—A. T. R.

Survival of the mammalian testis in vitro. Lundy (C. J.), J. Am. M. Ass. (Chicago), 1925, **84**, 746–748.

Lundy has endeavored to determine the length of time that
may be permitted between the removal of the testis from the donor
and a successful graft made into the recipient. He transplanted
slices of testis tissue as well as the whole testis of adult white rats
immediately after, 24 hours after, 48 hours after, and 72 hours
after removal from the donor. The site of transplantation was in
the scrotal sac within the tunica vaginalis. Autoplastic and homo-
plastic transplantations were made into completely castrated male
animals. Observations on the motility of the spermatozoa were
made immediately, 24, 48 and 72 hours after removal of the testes
from the donor, warmed to 37° C., and examined by the hanging
drop method. Twenty-four hours after removal of the testes from
the body a few of the spermatozoa were slightly motile. Instead of
darting back and forth, they remained in the same relative position,
and their tails moved sluggishly from side to side. Forty-eight
hours after removal no motility was observed. As to the viability
of the testis tissue of the rat, it was found that when preserved 24
hours or longer outside the body, it cannot be used for successful
transplantation.—A. M. A.

Lipoids in testes of children (Lipoiduntersuchungen im kindlichen
   Hoden). Oppermann (E.) & Jaffé (R.), Ztschr f. Konstit.
   (Berl.), 1924, 10, 111-120.

A study based on the testes of over 50 boys, from newborn
babies to 16 years of age. Only small amounts of glycerinesters
were found in the interstitial cells during the first two weeks of
life. In children from 1 to 9 months of age that died of acute
diseases the abundant interstitial cells contained also cholesterin
and fatty acid compounds. In marasmus the authors found glycer-
inesters instead of cholesterinesters, while in accidental death (all
over 2 years of age) no lipoid was found in the interstitial cells.
However, when the germinal epithelium begins to mature in such
cases, phosphatides and cerebrosides appear in these cells. In
chronic diseases the abundant intertubular tissue is free from lipoid-
containing interstitial cells. The authors do not believe in the
trophic function of the interstitial cells.—A. T. R.

The production of certain distinct types of reactions by the use of
   ovarian extracts. Papanicolaou (G. N.), Proc. Soc. Exper. Biol.
   & Med. (N. Y.), 1924, 22, 106-108.

Corpora lutea of pigs and cows were used and the extract tested
on guinea pigs, particularly by watching the changes in the estrous
cycle. Three effects were noted, produced presumably by three dif-
ferent hormones. (1) Extracts of corpus luteum of a lipoid nature

of age is tabulated. The results are much alike in the two species.
—A. T. R.

A case of Fröhlich's syndrome. Abrahamson (L.), Irish J. M. Sc. (Dublin), 1925, 5s. No. 37, 58-62.

The case, that of a 17-year-old boy, appeared to be typical except that the sugar tolerance instead of being increased was distinctly diminished.—R. G. H.

The effect of pituitrin on blood and on lymph and urine production. Bayley (E. C.), Davis (J. C.), Whitman (W.) & Scott (F. H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 22, 312-314.

In 20 dogs tested with pituitrin injections, the blood concentration changed but slightly. The flow of lymph from the thoracic duct was very markedly decreased. The flow of urine was reduced and then markedly increased. These results indicate that the capillaries and kidney cells were rendered less permeable but that in the kidney the increased blood pressure eventually more than counterbalanced this.—J. C. D.

Purine metabolism in diabetes insipidus (Sur le métabolisme des purines dans le diabète insipide). Eliane Le Breton & Kayser (C.), Compt. rend. Acad. d. sc. (Par.), 1924, 179, 1218-1219.

The excretion of purines other than uric acid parallels the degree of polyuria, and the ratio of uric acid to hypoxanthine is smaller, the more intense the polyuria.—A. T. C.

Juvenile adiposity. Engelbach (W.), Ann. Clin. Med. (Balt.), 1924, 3, 198-208.

This paper describes a series of cases of juvenile adiposity shown before the American Congress of Internal Medicine. The condition, it is pointed out, is extremely common, but, as children do not tend to suffer from any other complaints at this age, except their physical abnormality, it is often left untreated. Good results can be obtained in pituitary cases by treatment with pituitary extract, and the author claims that the results obtained in one-third of his cases are as striking as those produced by thyroid administered in myxedema. They are not, however, so constant on the whole, for the late diagnosis and late institution of treatment, often many years after the gland has begun to function abnormally, preclude this. He suggests that 70-80% of cases of juvenile adiposity are of pituitary origin, and that the real importance of the adiposity at this age is not so much the cosmetic effects or inconvenience of overweight as the danger signal indicating insufficiency of the

anterior lobe, which controls to a large extent the osseous growth
and the development and function of the genital system. Conse-
quently such obesity should be regarded as a suspicious sign and
treatment should be instituted. If this were done, the author sug-
gests that the number of individuals who go through the adolescent
period without proper development and function of the generative
organs would be considerably diminished.—*Med. Sc.*, **11**, 168.

Secondary female hirsuteness, a hypophyseal characteristic (Die
    sekundäre weibliche Behaarung, ein Hypophysenmerkmal). Oli-
    vet (Jeannet), Ztschr. f. Konstit. (Berl.), 1924, **10**, 268-280.

From clinical cases and experimental evidence, Olivet concludes
that the "male" type of hair distribution over the face and body is
a specific sex characteristic dependent upon the testes, while the
"female" type (finer and less extensive) is really an asexual type,
development of which is dependent upon the hypophysis and hence
is modified in hypophyseal disorders. Literature is cited.—A. T. A.

A clinical study of deficient anterior pituitary functioning in women.
    Perkins (J.), Boston M. & S. J., 1924, **191**, 973-977.

Thirty-one cases are tabulated to show the occurrence in them
of different symptoms. Anterior lobe substance apparently gave
relief in some of these cases.—J. C. D.

Blood sugar studies in experimental pituitary and hypothalamic
    lesions. Sachs (E.) & MacDonald (M. E.), Arch. Neurol. &
    Psychiat. (Chicago), 1925, **13**, 335-368.

An experimental study of blood sugar values in the dog fol-
lowing removal of the hypophysis and lesions of the hypothalamic
region was carried out. The lateral approach of Cushing and
Paulesco was used. Protocols of 35 operated animals are reported,
with blood sugar values, blood sugar tolerance curves, urinary find-
ings, clinical symptoms and postmortem histologic findings. The
experiments indicated that complete removal of the pituitary, if the
hypothalamus is not injured, does not lead to the death of the
animal. Deaths that occurred were always associated with hypo-
thalamic injury. These experiments confirm the work of others
that polyuria is apparently due to hypothalamic injury. The blood
sugar average in fasting animals is slightly lower after pituitary
or hypothalamic operation, but this may be within normal limits
of variation. Transient glycosuria for from one to two days oc-
curred after hypothalamic puncture in a few cases, and during this
time the blood sugar was higher than normal. Because of the
transience of this symptom, the investigators do not consider it of

great importance. The height of the blood sugar curve following operation, in all cases except those of anterior lobe removal, was reached at the end of one hour, in contrast to the curve in normal animals in which the height occurs at the end of one-half hour. The blood sugar curve in the cases of anterior lobe removal was of the normal type. The authors were unable to produce permanent glycosuria experimentally, although it has been observed in cases of pituitary disease. Some, but not all, of these were cases of hyperfunction of the anterior lobe, which, it is stated, can not be produced experimentally.—R. G. H.

Changes in the hypophysis in chronic inanition (Über die Änderungen in der Hypophyse bein chronischen Hungern). Sedlezky (S. K.), Ztschr. f. Konstit. (Berl.), 1924, **10**, 356-366.

The developing human hypophysis in chronic inanition, which in general was an accompaniment of various serious diseases, shows loss in weight of the organ as a whole, hypoplasia of the glandular portion, reduction in eosinophilic cells and an increase in colloid. The necrosis in the pars anterior is characterized by basophilic granulation. The basophilic cells increase. Hyperemia is evident. Most of these changes also occur in the fully developed hypophysis in chronic inanition. However, only about 20 cases of all ages were observed. Post-mortem examination was made one and two days after death and the weights of other organs, including most of the ductless glands, are tabulated. Some literature is cited.

—A. T. R.

Further studies on the bio-assay of pituitary extracts.—The action of standard infundibular powder on the secretion of urine. Smith (M. I.) & McClosky (W. T.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **24**, 371-389.

A desiccated and defatted infundibular powder was found to have renal effects similar to the fresh gland extract. In anesthetized rabbits the augmentation lasted about one-half hour, often preceded by a short period of urinary suppression and sometimes followed by a more lasting diminution of flow. In non-anesthetized animals and in the human subject pituitary extract produced a more lasting diminished urinary output.—G. E. B.

On the dialysis of the physiologically active constituents of the infundibulum. Smith (M. I.) & McClosky (W. T.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, **24**, 391-403.

The diffusion rates of the oxytocic, pressor and renal principles in infundibular extracts were found to be similar. This further indicates their chemical identity as held by Abel.—G. E. B.

Cessation of diabetes insipidus on roentgen-ray treatment of pituitary gland. Towne (E. B.), J. Am. M. Ass. (Chicago), 1924, **83**, 2085-2087.

The evidence presented suggests that a cure of diabetes insipidus was effected as a result of recession of a pituitary tumor under roentgen-ray treatment. It is said to be the first case of the kind on record. This patient suffered from diabetes insipidus, associated with one definite sign of a lesion in the vicinity of the optic chiasm—a defect in the upper temporal quadrant of the right visual field. A diagnosis of pituitary tumor was made, and the patient was treated by roentgen-ray crossfire to the pituitary region, in hope of causing recession of the tumor. Three months later the visual fields had returned to normal and have remained so. The urinary output dropped from about 8 liters to about 3.5 liters in the first three months; there was a recurrence at the fifth month which again appeared to respond to the roentgen ray; and there was another recurrence and similar, though slower, response beginning in the eighth month. Seventeen months after treatment was started, the output dropped to 2.5 liters, and it has remained at about that point until the present time, over three years after the patient came under observation. Very striking improvements and relapses in the physical and mental condition of the patient coincided with the drops and rises of the urinary output. The net result, clinically, is that a totally incapacitated man has become an efficient wage-earner.

—A. M. A.

Therapeutic uses of the parathyroid gland. Berkeley (W. N.), Boston. M. & S. J., 1925, **192**, 296-298.

From observations on several hundred cases made by different physicians and covering a period of 19 years, the author claims that parathyroid medication is distinctly helpful in paralysis agitans.

—J. C. D.

Disappearance of an old genital atrophy after ingestion of large quantities of fresh thymus (Disparition d'une atrophie génitale ancienne après ingestion de grandes quantités de thymus cru). Camus (J.) & Gournay (J. J.), Compt. rend. Acad. d. sc. (Par.), 1924, **178**, 673-674.

A dog with experimental diabetes insipidus from a lesion at the base of the cerebrum showed after 4 years considerable obesity and complete genital atrophy. Feeding fresh thymus led to no change in weight or in the degree of polyuria, but the genital atrophy disappeared.—A. T. C.

A case of tetany treated with parathyrin. Collip (J. B.) & Leitch
(D. B.), Canad. M. Ass. J. (Toronto), 1925, **15**, 59-60.

A female child, aged 22 months, with pronounced rickets, de-
veloped characteristic tetany during an attack of broncho-pneumo-
nia. "Parathyrin," given daily subcutaneously and then by mouth,
caused disappearance of all signs of tetany within 24 hours. There
was no sign of recurrence during 14 days' treatment and 7 subse-
quent days without treatment.—A. T. C.

**Perlingual administration of insulin (L'administration perlinguale
de l'insuline).** Blum (L.), Compt. rend. Acad. d. sc. (Par.), 1924,
178, 1225-1226.

Positive results (lowered hyperglycemia) are produced with
extremely concentrated preparations, but are less constant than
when insulin is injected.—A. T. C.

**Generalized edema immediately following insulin control in diabetes
mellitus.** Gibson (R. B.) & Larimer (R. N.), J. Am. M. Ass.
(Chicago), 1925, **84**, 491-492.

A pronounced generalized edema occurring in diabetic patients
immediately following desugarization of the urine with insulin
therapy was observed five times last year in the clinic with which
Gibson and Larimer are connected. The edema promptly disap-
peared after treatment with potassium bicarbonate and potassium
chlorid, 0.6 gm. each, three times a day, with meals. No recur-
rence of the edema had been reported by the patients when the
potassium therapy was discontinued on discharge. None of the
patients had significant renal or cardiac disturbances. The urines
of all the patients were free from acetone and diacetic acid when
the edema developed. That the edema may persist for thirty days if
uncontrolled was shown in one case; potassium therapy was then
instituted, and the edema almost completely subsided in thirty-six
hours.—A. M. A.

**Administration of insulin by mouth especially from the point of
view of the age of the patients and the condition of the stomach
(De quelques essais d'administration de l'insuline par voie buccale
spécialement au point de vue de l'âge des patients et de l'état fonc-
tionnel de l'estomac).** Gjertz (E.), Acta med. Scand. (Stock-
holm), 1925, **61**, 295-300.

The experiences of 6 patients are reported, 3 diabetics ranging
in age from 9 to 21 years, and 3 others, aged 41 to 47 years, having
achylia gastrica or diminished HCl. Two of the latter were dia-

betics also. A marked difference was noted between the two groups. Three hours (in one case only 2 hours) after ingestion of insulin in oil or in water the blood sugar was lowered in those of the first group 0.040 to 0.058 per cent, while in the second it was lowered only 0.016 to 0.020 per cent. This cannot be explained merely by the different reaction of the two groups to fasting. It is shown that in young diabetics insulin causes diminution of sugar in the blood when a similar diminution is not manifested in older patients and those in whom the gastric secretion is altered. Larger doses of insulin were administered to one patient in each of the two groups to determine whether larger doses of insulin would cause greater diminution of the blood sugar. Uniform results were not obtained, however.—Author's summary.

Does insulin significantly affect the blood concentration? Hamilton (W. F.), Barbour (H. G.) & Warner (J. H.), J. Pharmacol. & Exper. Therap. (Balt.), 1924, 24, 335-337.

Convulsive doses of insulin given to normal dogs and rabbits failed to alter materially the total solids or the specific gravity of the blood.—G. E. B.

Action of insulin on the basal metabolism of the totally depancreatized dog (Action de l'insuline sur le métabolisme basal du chien totalement dépancréaté). Hédon (E.) & Hédon (L.), Compt. rend. Acad. d. sc. (Par.), 1924, 178, 1633-1635.

A five months' experiment with a totally depancreatized dog showed that if insulin treatment with proper diet be sufficiently prolonged a normal condition of nutrition can be completely restored.
A. T. C.

The action of insulin in the frog and some vertebrates. Hemmingsen (A. M.), Skandin. Arch. f. Physiol. (Leipz.), 1924, 46, 56-63.

The blood sugar of the frog is reduced after insulin injection. In butterfly larvae the total reducing power of the blood rises after giving insulin. In neither animal does it change the rate at which injected sugar disappears from the blood stream. No convulsions were observed. Two and one-half hours after injection of insulin into butterfly larvae the respiratory quotient rose, probably indicating an increase in carbohydrate metabolism.—G. E. B.

Some observations on insulin; its effect on the isolated heart and its therapeutic action (Einige Angaben über das Insulin: seine Wirkung auf das isolierte Herz und seine therapeutische Anwendung). Kogan (V. M.), Ztschr. f. d. ges. exper. Med. (Berl.), 1924, 42, 25-40.

Many observers have studied the antagonism existing between adrenalin and insulin in their effect on the blood sugar. Experiments have also been carried out on the influence of insulin on the isolated heart, but though an increased removal of sugar from the circulating fluid has been shown, no effect on the heart's beat has been previously noted. The author has now studied the action of insulin on the heart, and finds that there is a marked influence on the beat, the systolic amplitude being increased and the pause lengthened. Adrenalin and insulin are not only antagonistic, therefore, in their effect on blood sugar, but also in their action on the beat of the heart.—Med. Sc., 11, 97.

Theory of insulin action (Theorie der Insulinwirkung). Laufberger (V.), Klin. Wchnschr. (Berl.), 1925, 4, 151-154.

Laufberger shortened the life of rabbits poisoned with insulin by forcing them to run. Frogs kept for 14 hours daily at a temperature of 24 C. died within 4 days when injected daily with one-tenth of the dose necessary for a rabbit. Frogs kept in a cool room showed no disturbance after 20 days, but died in about 3 hours when brought into a warm room. The increased amount of lactic acid in the blood depends on the exertion and not on the action of insulin. The phenomenon can be demonstrated also on isolated extremities of an animal. Insulin does not inhibit the formation of glycogen from glucose and dioxyacetone. It prevents the change of proteins and fats into glucose. The respiratory quotient after ingestion of a mixture of alcohol and glucose is not influenced by insulin. This indicates that it does not enhance the oxidation of sugar. The increased utilization of sugar by the surviving heart and the increased respiration of tissues after insulin are admitted. Yet the author points out that other substances—especially other hormones —produce the same effect in isolated tissues. The really specific action of insulin can be observed only on the whole organism. No proof of an increased cleavage of carbohydrates in the intact organism by insulin has been presented. Its inhibiting action on the new formation of carbohydrates from other substances is, in his opinion, the essence of its action.—J. Am. M. Ass., 84, 861.

The effect of insulin on the morphological blood picture. Levine (V. E.) & Kolars (J. J.), Proc. Soc. Exper. Biol. & Med. (N. Y.),. 1925, 22, 169-170.

In rabbits there is an increase in the number of red and white cells per cc. after insulin. The increase of the white cells is proportionately greater than that of the red. The change in count follows

the fall in blood sugar.   Anhydremia with mild leucocytosis would account for these changes.—J. C. D.

Diabetic cataracts in an infant.   Major (R. H.) & Curran (E. J.), J. Am. M. Ass. (Chicago), 1925, **84**, 674.

Major and Curran report the case of a boy, aged 11 months, who was admitted to the hospital because of the presence of sugar in the urine. Six months before admission, the mother noticed that the child became restless, and that his eyes began to get dark and were changed in appearance. The physical examination showed marked emaciation. The skin was somewhat yellowish. He was very fretful and cried constantly. Both eyes showed a marked lateral nystagmus, and the lenses of both were almost opaque and milky white in appearance throughout, excepting that there were two small areas in the left lens which were a little clearer than the rest of the lens. These ultimately became opaque. This patient was placed on a diet of whole cow's milk, 5% vegetable purèes and cod liver oil, and was given from 6 to 10 units of insulin a day A discission of each cataract was done, and the nucleus lifted into the anterior chamber to facilitate absorption. The cataracts had the appearance of those found in young diabetic patients and were certainly not congenital in origin, for as time went on they became denser. Six months later the patient was readmitted to the hospital, and at that time showed complete clearing up of one of the cataracts and almost complete disappearance of the other. The vision was apparently normal; the nystagmus had disappeared. Three blood sugar determinations showed 67, 127 and 80 mg. per hundred cubic centimeters. The boy at this time was taken off insulin. Recent letters from the patient's mother state that he is getting along very well with slight restrictions of diet and small doses of insulin, from 2 to 3 units a day. This is apparently the youngest diabetic patient on record suffering from cataracts. Other very striking features of his illness were the rapid increase and equally rapid lowering of tolerance from time to time.—A. M. A.

Insulin incred galvanic excitability (Insulin und Galvanische Erreg-
ꞏ   Waltner (K.), Klin. Wchnschr. (Berl.), 1925, 4, 168.
ome observatꞏ
its therapeuti.   ᵉsted tʰe galvanic excitability of six children ranging
in wirkung auf   months to 10 years. All had "cathode opening con-
tracꞏꞏ endung).   ᵗhan 5 M. A. Under the influence of insulin along
with aꞏꞏ   1924, 42,ᵒod sugar appeared an augmentation of the gal-
raꞏꞏc exꞏꞏꞏ   hese iń general ran parallel, though the effect

on excitability came on somewhat more slowly and lasted somewhat longer. The mechanical excitability was similarly affected.—R. G. H.

Some cases of diabetic coma complicated with uraemia, and some remarks on the previous history of the diabetic coma. Warburg (E.), Acta med. Scand. (Stockholm), 1925, **61**, 301-330.

The first case was described by v. Stosch in 1828. From a review of the literature and a metabolic study of 4 patients Warburg concludes that acute degeneration of the kidneys with great insufficiency occurs in some cases of diabetic coma. The albuminuria is often slight in these cases. The blood sugar is not infrequently extremely high, while the glycosuria is relatively low. Diacetic acid and acetone may be absent in these cases. In a number of cases the respiration is not of the "typical" hyperpnoeic form. The kidney degeneration is cured, at any rate partially, by insulin treatment. It is necessary to treat coma cases very early and very energetically in order to avoid cardiac and renal complications. Heart tonics and diuretics are of considerable value as adjuvants in conjunction with the pancreatic hormone. An excellent working bibliography is included.—R. G. H.

Hydremia of diabetes treated by insulin (L'hydrémie au cours du diabète traité par l'insuline.) Widal (F.), Abrami (P.), Weill (A.) & Laudat, Compt. rend. Acad. d. sc. (Par.), 1924, **178**, 2144-2145.

Insulin produces a definite upset of water equilibrium, with blood dilution, shown by fall of serum albumin. The effect sets in suddenly within 24 hours, and persists, although insulin treatment be stopped.—A. T. C.

Progressive and regressive forms of Hassall's corpuscles (Über progressive und regressive Formen von Hassallschen Körpern). Hammar (J. A.), Ztschr. f. Anat. u. Entwcklngsgesch. (Berl.), 1924, **70**, 466-488.

After giving a detailed description of the histological characteristics of both developing and degenerating forms of Hassall's corpuscles, Hammar lists Basedow's disease, various types of infection and snake bite (all characteristics of toxic factors) as conditions causing an increase in these corpuscles, probably from enlargement of reticular cells. Degenerated forms are noted especially in inanition and diseases caused by nutritional disturbances, as in cardiac failure, blood diseases, and perhaps also in epilepsy and eclampsia. Hammar stresses the significance of the regeneration of the corpuscles in connection with thymic function. Literature is cited.—A. T. R.

The presence and significance of lipoids in the thymus (Über das Vorkommen und die Bedeutung von Lipoiden im Thymus). Kyrilow (A.), Ztschr. f. Konstit. (Berl.), 1924, **10**, 460-481.

Kyrilow reports an investigation of the thymus from 34 cattle varying in age from 2 fetal months to 9 years, including 6 pregnant cows of the same age. In this species there are very few Hassall's corpuscles. Another unique feature is the presence of a special "infiltration cell." The author also examined 95 human thymus glands from premature and still-born subjects to persons past the climacteric stage, including 10 cases of pregnancy. Cholesterin mixtures in the intrathymic adipose tissue increases with age. Phosphatides are regularly present in Hassall's corpuscles. Fat is also found in certain reticular cells and eosinophilic leucocytes within the thymic parenchyma except during pregnancy. These fat-laden cells are also generally absent in climacteric women and those suffering from amenorrhea. There appeared to be no correlation between the lipoid content and the particular diseases, although in three cases of uremia unusually large fatty Hassall's corpuscles were present. Literature is cited.—A. T. R.

The treatment of the complications arising after operations on the thyroid gland. Clute (H. M.), Boston M. & S. J., 1924, **191**, 1147-1151.

The article is based on 1376 operations. The author concludes that although most patients have an uneventful recovery, those complications which may follow any surgical procedure occur at times in operations upon the thyroid gland. These complications are treated on the general surgical principles now well established. Complications arising from increased thyroid secretion should seldom arise if the proper operative procedure has been chosen. Mediastinitis is the most serious complication following thyroidectomy. Recurrent laryngeal nerve paralysis may rarely occur from injury to one nerve. A bilateral paralysis should never occur. Cases of hyperthyroidism should have repeated metabolism tests after operation in order to be certain that their metabolic rate is normal, as only in this way can we be certain that they are cured.—J. C. D.

Preparation of an antithyroid serum and its biological properties (Préparation d'un sérum antithyroïdien; ses propriétés biologiques). Coulaud (E.), Compt. rend. Soc. de biol. (Par.), 1925, **91**, 920-922.

Coulaud attempted to produce a cytolytic serum for the thyroid gland. Fresh sheep thyroid was ground finely in a mortar, using aseptic precautions, and physiological salt solution added. After

allowing the suspension to settle the supernatant fluid was injected intravenously into sheep 4 to 6 times at 2 day intervals. Serum obtained 45 days later had a marked effect on the thyroids of rabbits into which it was injected. It caused a disappearance of colloid and a reversion to the fetal condition. By the complement deviation method no antibody could be detected.—R. G. H.

The effect of iodine on hyperthyroidism in man. Cowell (S. J.) & Mellanby (E.), Quart. J. Med. (Oxford), 1924, 18, 69.

The relationship between the iodine content of the thyroid gland and the occurrence of the symptoms of hyperthyroidism in man is discussed. Reports are given of a series of cases of hyperthyroidism treated with small doses of iodides. In every case clinical improvement was observed, accompanied by a fall in the basal metabolic rate and pulse rate. This improvement reached a maximum in from 10 to 20 days, and was then frequently followed by a gradual return of symptoms, which did not, as a rule, attain their former severity. The withdrawal of iodides from these patients, even when they had been receiving it continuously for several months, was followed by an exacerbation of symptoms which could be relieved by once more giving iodide. The authors conclude that in cases of hyperthyroidism the action of iodine is not merely concerned with the elaboration of thyroxin and the conversion of hyperplastic thyroids into colloid-containing ones, but that it influences metabolic processes in ways not at present understood.

—Physiol. Abst., 9, 540.

Myxedema heart. Fahr (G.), J. Am. M. Ass. (Chicago), 1925, 84, 345-349.

Fahr states that in myxedema there are definite objective signs as well as subjective symptoms of heart failure which may be present for many years, and which do not respond completely to the therapy of rest and digitalis but which are cured by thyroid medication. Characteristic of "myxedema heart" are an enormous dilatation of all chambers of the heart and absence of negativity of the T wave of the electrocardiogram in Lead I. The dilatation of the heart disappears rapidly, and the T wave becomes positive under thyroid medication. During the transition from a negative to positive T wave, we may get a stage in which the T wave is diphasic. A few cases show the split and prolonged Q-R-S group of delayed intraventricular conduction. This abnormality also disappears under thyroid medication. All of our patients showed a negative Q-R-S group in Lead III during the stage of marked cardiac dilatation. The negative Q-R-S group in Lead III, thought by many to be char-

acteristic of, left ventricular hypertrophy, becomes positive in these cases after thyroid medication, thus proving for these hearts that a negative Q-R-S group in Lead III is not due to a preponderance of musculature of the left ventricle.—A. M. A.

Thyroid and nitrile poisoning (Schilddrüse und Nitrilvergiftung). Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1923, 200, 571-582.

Experiments with KCN, acetonitrile and propionitrile resulted in no support for a detoxication theory of thyroid function, since thyroidectomized mice showed greater resistance to KCN and propionitrile than normal controls. Acetonitrile is not a specific reagent for thyroid activity, since feeding thyroid, pituitary or testicular hormones also increases resistance to this poison.—A. T. C.

The influence of intestinal bacteria upon the thyroid gland. Harries (D. J.), Brit. M. J. (Lond.), 1923, i, 553-555.

The flora of the intestine can be subdivided into two groups, acid producers and indole producers. The indole producers are absent in exophthalmic and present in parenchymatous goiter, but in the latter the effects appear to be the result of the inability of the thyroid to use the material at its disposal rather than an undue destruction of tryptophane.—Physiol. Abst., 9, 540.

The inverse relation of iodin and goiter in Utah. Hathaway (J. C.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 22, 183.

Utah is on the edge of the goiter belt. It is found that the incidence of goiter in school children bears an inverse relation to the amount of iodin in the drinking water.—J. C. D.

A case of hypernephroma associated with thyroid hyperactivity. Kaufmann (J.) & Cashin (M. F.), Canad. M. Ass. J. (Toronto), 1925, 15, 37-40.

As the hypernephroma extended the thyroid, already unbalanced by an adenoma, became suddenly toxic. Death occurred from thyroid hyperactivity and hypernephroma, toxicity of the one progressing proportionally to the destruction of the other.—A. T. C.

A quantitative study of the physiologic action of thyroxin. Kendall (E. C.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 22, 307-308.

An analysis of the structural formula of thyroxin as related to its oxidizing action. The function of thyroxin is to furnish a compound that can be acted on by mild oxidizing agents, among which is molecular oxygen, and which can then by an intramolecular rearrangement produce an intensely oxidizing substance.—J. C. D.

Studies on compensatory hypertrophy of the thyroid gland. Loeb
(L.) & Kaplan (E. E.), J. Med. Research (Bost.), 1924, 44, 557-
578.

This paper describes a series of experiments which were carried
out to throw further light on the relationship between the thyroid
gland and the anterior lobe of the pituitary. Evidence that such a
relationship does exist rests on two sets of observations and experi-
ments: (1) those concerning the effect of the extirpation of one
gland upon the other; (2) those concerning the effect of the admin-
istration of these glands on metamorphosis in amphibia. These
experiments have shown that in amphibia the anterior lobe of the
pituitary increases growth, and that even oral administration of this
substance is effective; also that the anterior lobe of the pituitary
contains a substance which hastens metamorphosis in amphibian
larvae. After studying this evidence, the possibility was suggested
to the authors that the administration of anterior lobe of the pitu-
itary might exert some influence on the hypertrophy of the thyroid
gland which develops in the guinea pig after extirpation of the
greater part of this organ. It was also thought that the effect of
administration of anterior lobe of pituitary on compensatory hyper-
trophy of the thyroid might constitute a valuable indication of the
relationship of these two glands. Consequently, the series of experi-
ments described in this paper were undertaken. A comparison was
made between the compensatory hypertrophy following extirpation
of the greater part of the thyroid gland in control guinea pigs kept
on ordinary food, and the hypertrophy in guinea pigs which, after
extirpation of the greater part of the thyroid gland, were fed, in
addition, daily with one 5 gr. tablet of anterior pituitary (Armour
& Co.). The results of a large number of experiments are given in
detail, and show that in the guinea pig the administration of ante-
rior lobe extracts by mouth prevents entirely, or almost entirely, the
compensatory hypertrophy of the thyroid gland, which in a consid-
erable number of cases does follow the extirpation of the greater
part of this organ. The authors suggest that this effect is not
caused by the admixture of inorganic salts of iodine with the prep-
aration, because, as they are proposing to show conclusively in a
subsequent communication, iodine in inorganic form is unable to
prevent compensatory hypertrophy in the guinea pig.

—Med. Sc., 11, 257.

Iodin and goiter. McGuire (S.), South. M. J. (Birmingham), 1925,
18, 87-91.

Following the use of Lugol's solution by mouth in 50 cases of
exophthalmic goiter McGuire concludes that pre-operative mortality
can be reduced and desperate cases can be converted into good

surgical risks. Preliminary ligation can be practically abandoned if iodin is administered. Post-operative hyperthyroidism can be controlled. The present low mortality of thyroidectomy can be reduced despite the acceptance of risks previously declined. Mild cases can be relieved of symptoms and possibly tided along until there is spontaneous cure without operation. Patients that have had relapse after operation can be benefited and perhaps cured.
                                                              —R. G. H.

The oculo-cardiac reflex and endocrinology. Oliver (J.), & Oliver (G. Y.), Edin. M. J., 1925, N. S. **32,** 69-71.

Pressure on the eyeball changes the pulse rate, slowing it in vagotonic and increasing it in sympathotonic individuals. This is, in the authors' opinion, helpful in diagnosing hyperthyroidism and hypothyroidism.—J. C. D.

Roentgen ray therapy in thyroid disturbances (Indicaciones y contraindicaciones de la Roentgenterapia en los transtornos anatomofunctionales del tiroides). Piga (F.) & Larrú, Siglo méd. (Madrid), 1923, **71,** 837-840.

A bibliographic resumé of this subject is given, from which the deduction is made that roentgen ray therapy may be indicated in a great number of cases of hyperthyroidism. A careful study of the symptoms in many such cases, however, shows that this treatment is directed solely to hyperthyroidism and not to other accompanying symptoms which merit attention. In all such cases a study should be made of the basal metabolism, thus proving the efficacy of roentgen therapy. In cases of goiter with compressional disturbances, radiotherapy is of no avail. Surgical measures ought to be carried out without delay. When goiter is associated with hypertrophy of the thymus there is little hope in radiotherapy; treatment of the thymus is required.—E. B.

Pulmonary tuberculosis and exophthalmic goiter (Tuberculosis pulmonar y bocio esóftalmico). Plasco (N.), Rev. de hig. y de tuberc. (Valencia), 1923, 182, 189, 194.

The coexistence of pulmonary tuberculosis and exophthalmic goiter is seldom observed. On the other hand, pulmonary tuberculosis is often wrongly diagnosed as Graves' disease, due to symptoms of thyroid origin, such as tachycardia, palpitations, irritability, trembling, slight thyroid hypertrophy, etc. The author describes 6 cases of pulmonary tuberculosis and hyperthyroidism. In all of these cases it was noticed that the tubercular lesions became more pronounced with the appearance of thyroid hyperfunction.—E. B.

The effect of thyroidectomy on the calcium content of the blood serum. Rabinowitch (I. M.), J. Lab. & Clin. M. (St. Louis), 1924, 9, 543-546.

A decrease in calcium content of the blood serum following thyroidectomy was noted in 26 cases. The decrease was not of sufficient degree to produce tetany. As no parathyroid tissue was found in the portions of the thyroid removed, the author concludes that the phenomena is due to trauma during manipulation in the parathyroid regions.—I. B.

The effect of iodin in exophthalmic goiter. Starr (P.), Walcott (H. P.), Segall (H. N.) & Means (J. H.), Arch. Int. Med. (Chicago), 1924, **34**, 355.

These authors studied the effect of Lugol's solution in exophthalmic goiter, administering 15 minims daily. Twenty-five patients were treated identically, and pathological reports of the thyroid gland were obtained from all but two. Hyperplasia without adenomata was observed. This proves that proper subjects were selected in order to test Plummer's views on the rôle of iodin in exophthalmic goiter as opposed to adenomatous goiter with hyperthyroidism. Eighty per cent of these subjects responded to iodin by a more or less extensive remission of the disease, as indicated by drop in basal metabolism and pulse rate and gain in weight. The remission was found to be often as rapid and as extensive as that following subtotal thyroidectomy. The authors believe that the iodin administered was the cause of the remissions. But iodin alone (as Lugol's solution) was not found to cure or suppress the disease permanently. After a patient has been taking iodin, a rapid rise of metabolic rate and increase of toxic symptoms will occur within one or two weeks if the iodin is stopped. Therefore if iodin is used as a pre-operative preparation, no gap between medication and operation should be allowed to occur. Several excellent charts are included, illustrating iodin remissions and post-iodin reactions on basal metabolic rate, pulse rate and weight.—H. L.

Chemical and histological studies of goiter with special reference to cases of Graves' disease following iodine treatment (Chemische und histologische Untersuchungen an Strumen, mit besonderer Berücksichtigung von Jodbasedowfällen). Tobler (T.), Mitt a. d. Grenzgeb. d. Med. u. Chir. (Jena), 1924, **37**, 622-640.

The intensive campaign waged in recent years against endemic goiter in Switzerland, though on the whole strikingly successful, has had certain ill effects, especially in adults. The excessive use of iodine by the general population, without medical control, has resulted in a considerable increase in the prevalence of Graves'. disease. In the author's clinic the yearly admissions for this condition have risen from 6 to 40, and he is of the opinion that the

preparations at present employed for the prophylaxis of endemic goiter contain too large an amount of iodine. An analysis of the iodine content of 39 goiters removed at operation shows that the percentage of iodine was lowest in patients with true Graves' disease who had received no iodine medication, while it was very greatly increased in goiters removed from patients who had developed symptoms of hyperthyroidism as the result of intensive iodine treatment. In the latter group 10 gm. of the fresh gland showed on the average no less than 8.9 mg. of iodine, as compared with 0.09 mg. in goiters removed from patients who had developed Graves' disease spontaneously. Goiters from patients in whom symptoms of hyperthyroidism had resulted from iodine treatment present a variable histological picture. In the majority the characteristic features of Graves' disease are present, but others are absolutely indistinguishable from colloid goiters.—Med. Sc., 11, 257.

AN EVALUATION OF THERAPY,
WITH SPECIAL REFERENCE TO ORGANOTHERAPY*

LEONARD G. ROWNTREE, M.D.,

Division of Medicine, Mayo Clinic and The Mayo Foundation,
ROCHESTER, MINNESOTA.

The ideal medical treatment is built on the early recognition of disease; an understanding of its causes, its nature; the mechanism of its production, and the development of associated clinical manifestations; a knowledge of the character, extent, and probable outcome of the resulting functional and morphologic changes, and a correct evaluation of the symptoms and of the clinical and laboratory findings. It also demands an appreciation of the indications for treatment, the effect of treatment, and the best methods to employ for the prevention, abortion, amelioration or cure of disease. The goal in treatment can be reached only by the intelligent understanding of disturbed function, and the correction of such disturbance by the application of rational measures. Thus treatment becomes simply a matter of laws, and the "healing art" gives way to a healing science.

It is evident, therefore, that therapeutics is not simply a branch of medicine, but rather the fruit of the medical tree, the culmination of all that science can teach concerning the cause and cure of disease. But the goal is not attained as yet either in the field of general therapy or of organotherapy. Treatment is

still beset "by débris of broken systems and exploded dogmas." Perhaps it would be well to climb with Holmes his "Monte Testaccio" formed of "the shards and remnant of old vessels which once held human belief," and, as he suggests, gaze about us and broaden our horizons. To our advantage we might at the same time carefully determine the roads of progress in medicine and ascertain so far as possible what is retarding progress in the field of treatment.

Certain features of the landscape stand out in bold relief. Practically all roads of progress begin in the wilderness as by-paths. It is inspiring to look back over the roads that medicine has traveled and to study the lives of those masters, gifted with divine discontent and a spirit of achievement, who with rude axes blazed the bypaths that led onward to the relief of human suffering.

It was a long, dark road from the father of medicine and the versatile Galen to Harvey, the investigator, and to the observant Sydenham. It is since their day that we have learned how science measures, correlates, and advances from hypothesis to law. Therapeutics has not yet shaken off entirely the shackles of empiricism, but the application of law to treatment grows clearer as the cause of disease in illuminated. Disease itself is now recognized, and is treated earlier and more rationally. The therapeutics of today rests on the knowledge of yesterday; the investigation of today will find fruition in the therapy of tomorrow.

Into the chaos of medicinal treatment Schmiedeburg brought order. He gave us methods for the scientific investigation of drugs. As the outcome, we recognize that pharmacologic action is related to chemical constitution, and the field of specific chemotherapy has evolved. The discovery of antiseptics and various anesthetics has transformed a surgical operation from an adventure with death to a sane and safe procedure. Pharmacology has struck from the Pharmacopeia a host of useless drugs, has narrowed the realm of empiricism, and has firmly established relationalism in medicine.

Pasteur's discoveries, especially of the relation of micro-organisms to disease, great as they were in their immediate results, set the stage for the greatest achievement of medicine

of all time, the development of preventive medicine, "man's redemption of mankind." Nor without antisepsis and asepsis would we have modern surgery. Studies in immunology paved the way for many new diagnostic methods and for brilliant successes in treatment.

Without a knowledge of oxidation, life and its processes would still remain a riddle. It was left for a chemist, Lavoisier, to demonstrate that "la vie est une fonction chimique." A knowledge of the principles of metabolism, nutrition, growth, and the transformation of energy, is fundamental to biology, physiology, and medicine. The treatment of nutritional diseases demands the consideration of the caloric values of food and their energy exchange values, as well as of the part played by proteins, carbohydrates, fats, water, inorganic salts and vitamins, of which food is composed. Since Addison's day it has been established that metabolism is normally controlled, in part at least, by the glands of internal secretion, and that the disturbance of function of these glands initiates metabolic and nutritional disease. The field on which he threw the first glimmer is now broad enough to demand the earnest consideration of our entire profession, and the particular attention of such societies as ours.

In Virchows's cellular pathology the medical profession found a valuable anchor. It terminated that continuous and hopeless drifting, and inaugurated the fruitful investigation of organic disease. But any conception of disease, confined to structural and organic changes, is out of harmony with the facts and is also unsympathetic, if not actually antagonistic, to drug therapy. Such a narrow conception is responsible, to a large extent, for the therapeutic nihilism of the last generation. Already, recognition of functional elements and an appreciation of the part they play in disease have led to many successful methods of controlling deranged function. In fact, in many instances, not only the presence and extent of disease, but the efficacy of its treatment, is gauged today by tests of functional capacity.

No discovery in medicine, or any other science, sprang full-fledged, so to speak, from the loins of Jove. Each was the sum of earlier discoveries, added to and elaborated by, compre-

hending and original minds. Each master achieved less than the whole of his work, but often vastly more than he anticipated. From Newton, Liebnitz, Dalton and Maxwell, to Watts, Stephenson, Fulton and Edison, from Franklin to Marconi, from Curie to Rutherford, from Crooks to Roentgen; no work is ever complete, and when tired hands put it down, others pick it up. So interwoven are the threads of science that they all appear in the pattern of medicine. The energy of the steam engine is the energy of life; the law of the retort is the law of function; the struggle for existence throws light on disease.

The roads are still far from smooth, and progress is not unfaltering. Human incapacities and frailties, and professional limitations are more serious obstacles now than when progress depended only on the front line of workers. We can readily see that our forefathers erred in assigning the cause and cure of disease to supernatural agencies, in adopting speculative philosophy rather than the methods of science, in adhering blindly to authority, and in their persistent use of remedies about which they knew little, for disease about which they knew less. Yet which of us, being "wholly without sin," may venture to cast the first stone? It is more profitable and more just to visualize the chief barriers to advancement as they exist today, more especially those that retard progress in the field of treatment.

Our diagnostic limitations prevent us from recognizing, and hence treating, disease in its earliest stages. Function is usually disturbed before form is altered, and, obviously, deranged function is more easily corrected than altered structure. In not appreciating nature's defenses, the "vis medicatrix naturae," medical judgment has incorrectly gauged the results of treatment, and most of our therapeutic statistics have been vitiated by lack of adequate controls. The adaptation of measures of relief to the correction of deranged function necessitates a knowledge of the curative agent, as well as of the nature of the disease.

The failure of the leaders in medicine to show leadership in therapy is probably the chief cause of the therapeutic limitations of the profession. Only harm can follow further dependence on dictators in medicine. The leaders must show such breadth of vision, such comprehension of the whole field of medical science, as will stimulate the rank and file to emulation.

Not only the fruits of science, but science itself, must be the handmaiden of everyday practical medicine. The need is more pressing in therapeutics than anywhere else because treatment is set apart from pure science. Pharmacology stands too much alone. Therapy should carry behind it all the driving power that science can command. Only when the pharmacologist is brought to the bedside can he adequately test his theories in practice, in the flame of medical science. The internist should open the field of therapy to science and to scientists. Progress in therapy demands first-hand knowledge of its problems on the part of pharmacologists, physiologists, biochemists and physicists in order to obtain the most effective form of co-operation.

A physician fails individually as he falls short of the standards of his time. Lack of critical judgment or credulity in matters of therapy is, I believe, the chief cause of individual failure. Credulity is, in its essence, lack of wisdom; the physician who has failed may have received inadequate training in therapeutics. But more frequently he lacks the scientific habit of recording treatment and its effects, of measuring it objectively, and of checking his conclusion by controls. Sometimes he is constitutionally too optimistic and sees only the silver lining of the cloud of statistics. As often as not, he has used all his strength for the daily round and has none left to take to his "armchair of cogitation." Therapeutic judgment would be inestimably benefited by attention to these crucial matters, particularly the need of using accurate measurement whenever possible. Otherwise, although clinical observations may be very accurate, they cannot be utilized for further comparison. Laziness, slothfulness and carelessness, love of ease, lack of interest, also contribute prolifically to failure at times, but fortunately these are not common frailties among the practitioners of medicine.

The most pernicious influence in modern therapy comes from without, rather than within, the medical profession. Our best pharmaceutical houses attempt to meet the needs and supply the demands of modern scientific medicine, but there are still certain so-called pharmaceutical firms engaged in a most fraudulent exploitation of the medical profession and the public, in their greed for money. As a result, the physician finds himself

bombarded constantly by advertising matter, reeking with half truths and pseudoscientific patter unless he maintains a high threshold of suspicion he is likely to be seduced by these alluring falsehoods. Ridicule, as our weapon, does not suffice, for it falls unheeded on the thick skin of those who, in the guise of benefactors, betray the sick. The loathing of the conscientious physician should indeed break forth in a demand for federal investigation of much of the advertising material that comes to our desks. It would perhaps be difficult to prove intent to defraud, but it is a matter of right or wrong, and if willfully wrong should lead to prosecution. If prosecution is impossible we may at least notify those in authority and in the meantime use our waste baskets more extensively. Should we not in this Association establish through our official publication a department in which the duplicity and devious devices of these promoters and exploiters may be made apparent to the interested reader, as well as to responsible officials? Such a department could also serve to guide physicians in matters pertaining to organotherapy.

Endocrinology, as we know it, is a young science, but it has its roots in medieval lore. We observe medical history in the act of repeating itself. There is a tendency to bring endocrinology down to the level of the "conjectural art" of Celsus. We see endocrinology a fertile and recently discovered territory, with here and there patches undergoing cultivation; and already, under scientific leadership, several splendid avenues of progress leading to successful treatment. Still, vast areas are unexplored and uncharted. The same old influences are at work here, retarding, or even obstructing, progress. Advancement depends on a careful survey of the situation and the removal of all obstacles.

—— glands of internal secretion are concerned with growth, metabolism. They may be looked on '' but in regard to the exact func- a few facts and many fancies. shed facts of endocrinology may be These glands elaborate one or more fect physiologic activity. The hor- , are excreted in each instance into

the circulation and exert a specific action elsewhere in the organism. Disease of one of the glands may lead to increase, decrease, or disturbance of its activity, and this in turn may be manifested by acceleration, retardation, or perversion of physiologic functions in the organism. Disease may result from a lack of a specific hormone and, in certain instances, may be cured by its replacement with one of the same character; or an excess of hormone may cause disease which at times may be amenable to treatment through surgical procedures.

Investigation and discussion in this field have centered also about the possibility of correlated interaction or what might be termed pluriglandular interplay, and whether the various active principles act reciprocally, synergetically, antagonistically, or vicariously. Recently the question of modifying the nature of the active principles of the gland has come into the foreground.

In spite of the volumes written on the subject of organotherapy, only one principle of treatment, as Billings has said, has proved entirely successful in practice, and that is the replacement of a partially or completely missing hormone by one of the same nature. Although this method has been successfully applied to at least three or four diseases, it is not effective as yet in all diseases which are due to glandular deficiency. In this field splendid success has been attained with thyroxin and desiccated thyroid in the treatment of myxedema or cretinism in the young, with insulin in the treatment of diabetes, and with the extract of the posterior lobe of the hypophysis in the treatment of diabetes insipidus. Parathyrin promises equally good results in tetany, but even in these diseases treatment must be continuous. The only glandular substances uniformly effective when administered by mouth are those of the thyroid and the desicated gland, thyroxin. It should be admitted that beneficial results seem to be obtained at times in fields other than the three already mentioned, as for instance, in the treatment of Addison's disease by the Muirhead method. In such fields there exists legitimate opportunity for controlled experimentation, and such treatment must be looked on as more or less in an experimental stage. The results, good or bad, afford legitimate material for publication.

Certain glandular products, besides specifically influencing the organism, also possess definite pharmocologic properties which render them of unquestionable medical value, as, for instance, epinephrin, which stimulates the sympathetic nerve endings, and the extract of the posterior lobe of the pituitary which constricts capillaries.

In the field of organotherapy, too, progress is retarded by human frailties and professional limitations. Replacement or substitution therapy might have a much less restricted field of usefulness if it were not for those diagnostic limitations which make the evidence of deficiency in one or more glands difficult to recognize. Then we cannot be certain that the substance isolated from the gland represents its true, unaltered, active principle. Indeed we are not always certain that alleged products are even obtained from the glands in question. The dosage is bound to be inaccurate, and cannot be adjusted to the fluctuating needs of the organism, especially when the composition and potency of the preparation are uncertain. The greatest obstacle of all is the impossibility of copying nature's continuous administration of glandular products to meet the changing needs of the organism.

The attempt to control the overactivity of one gland by augmenting the action of another that may be antagonistic may be sound in principle, but so far it is scarcely more than speculative, and it is but little justifiable to expect the extract of one gland to correct functions that are not known to depend on that gland. Giving thymus substance for hyperthyroidism is not rational except as an experiment and even then should be preferably restricted to laboratory practice. But in fairness, it must be admitted that the improvement in general metabolism, resulting from thyroid medication, may at times indirectly correct underfunction on the part of the organism as a whole, and also perhaps of certain other glands of internal secretion. There is surely some connection between these organs, not understood, and sometimes quite remote. There is little consistency in the results obtained by most of the groping experiments in organotherapy, in spite of the statements in those very widely read, if unofficial, journals dedicated to human credulity. The methods

of Kendall, Banting, Collip, and Abel, more surely lead to success.

In organotherapy, human frailty looms large. Unfortunately, it must be admitted that in no other branch of medicine has its retarding and pernicious influence been more apparent than in the treatment of diseases of the glands of internal secretion. But the outlook in organotherapy is most hopeful. Success in its limited and legitimate field has been striking, in fact, little short of miraculous, and so encouraging that the field is now ardently exploited, both legitimately in the search for the elucidation of disease, and criminally by those who squeeze gold out of human heartaches. If we are to protect the public against unseasoned and immature conclusions, we must depend on reliable information only. Information concerning standard drugs can be obtained from the United States Pharmacopeia. New drugs of promise, introduced in an ethical manner, are accepted almost without delay by the Council on Pharmacy and Chemistry of the American Medical Association, and are listed and described in one of its annual publications, ''New and non-official remedies.'' Old and new ethical drugs, which are useful and reliable, are described in a small book, ''Useful Drugs,'' also published by the Council. The most flagrant offenders are exposed in the column of the Journal of the American Medical Association under the heading, ''Propaganda for Reform,'' under ''The Bureau of Information.''

The Council was created by the American Medical Association more than twenty years ago, with the idea of furnishing to physicians reliable information concerning drugs. Advertising space of the Journal of the American Medical Association and of most of the standard medical journals of the country is reserved for preparations accepted by the Council. Physicians are therefore safe in accepting such preparations as are advertised in the pages of the Journal of the American Medical Association, or in other high standard journals. Houses exploiting questionable and nonethical drugs, forced to adopt devious measures of advertising to reach the physician, flood him with circulars, pamphlets, and journals—so-called house organs—published by themselves.

The whole question of organotherapy has been very recently reviewed in a booklet containing the series of excellent articles that appeared in the Journal of the American Medical Association. The physician also must know where to secure these reliable drugs. The same publications contain sufficient information, if it is followed, to prevent the foisting of spurious products on the public. In specifying the products of particular firms, it is well to choose products of well established houses who advertise in the best journals and who are engaged in meeting the demands of the medical profession. The products of mercenary concerns who advertise in circuitous ways, who willfully misrepresent, and who attempt to create fictitious demands, should be shunned. Above all, flagrant boasters should be avoided, for, as Voltaire says, "It is only the charlatan who is certain."

There are a few simple rules to guide the general practitioner in the treatment of diseases of the glands of internal secretion. Glandular products should be used only as they are scientifically indicated, that is, as substitutional or replacement therapy. A single product of the gland concerned is to be given. This may suffice, provided the diagnosis is correct, the product potent, and properly administered. Fixed pluriglandular mixtures for so-called multiple glandular deficiencies are to be avoided. The practice of administering such mixtures constitutes a disgrace to twentieth century medicine, a menace to our profession, and a betrayal of our patients. When it is considered that the indications call for more than one principle, the second glandular product is administered in gradually increasing quantities. Accurate records of treatment should be kept and the results measured objectively.

As long as disease holds its challenge for prevention, abortion, amelioration and cure, the forces of investigation must toil on. The goal will only be reached through an intelligent understanding of disturbed function and the application of rational measures for its correction. The day is past when the student in the ward or the scientist in his laboratory may hope to expose the whole story of disease. The world of illness is our laboratory; science cannot be pre-empted. MacKenzie rose to eminence after carefully watching disease in his community for

many years. Any physician, a village doctor for half a life-
time, may be called to leadership if he uses the methods of
science. MacKenzie never ceased to preach the need of enrolling
the general practitioner in the army of progress. He depre-
cated the narrow conception of disease that comes only from
viewing the end result through a microscope. His efforts to the
last were concerned with the attempt to demonstrate the prac-
tical value of understanding early symptoms. As with diagnosis,
so with treatment. The response of advanced disease to therapy
is comparatively easy to determine; the response of disease at
its inception cannot be studied in the wards alone because the
hospital never hears the plaint of the slightly ill. In treatment,
now more than ever, progress depends on the co-operation of
every member of our profession in the application of the methods
of science to the problems of medicine.

CIRCULATORY DISTURBANCES IN DISEASES OF THE GLANDS OF INTERNAL SECRETION*

J. H. MEANS, M. D.
BOSTON

However obscure the functions of the endocrine glands may be we can agree, I think, that they are all concerned in one way or another, direct or indirect, with metabolism. If this is so, we must assume that they are likewise all concerned with the circulation, for in all except very lowly organisms the metabolism of tissue cells is vitally dependent upon a free supply of a suitable circulating medium. If the secretions of endocrine glands influence cell activities, they must of necessity also influence the supply of the medium upon which such activities depend. While the study of the exact mode of action by which such influence is brought to bear belongs properly to the physiologist or pharmacologist, it is altogether pertinent for the clinician to seek to interpret, in the light of knowledge gained by such studies, the circulatory disturbances which he may observe in patients known to be suffering from endocrine disease.

The actions on circulation which the several hormones may conceivably possess can be variously grouped. For convenience we may separate them into those affecting primarily the heart, the vessels, or the blood. Effects primarily on the heart may be manifest in the force, frequency or rhythm of the heart beat; those primarily on the vessels in the total or regional cross section of arteries, capillaries or veins; and those on the blood itself in its total quantity, viscosity, concentration, or ability to transport the respiratory gases.

To identify these effects in the patient, we are dependent upon the inferences which can be drawn from such factors as we can actually observe, measure and record. In man, for example, we can count the pulse, analyze cardiac conduction, and directly determine blood pressure, blood viscosity, and the chemical composition of the blood. Methods are also available for calculating indirectly the blood flow, both total and regional,

*Read before the Association for the Study of Internal Secretions, Ninth Annual Meeting, Atlantic City, May 26, 1925.

192

and the total volume of blood in the body. The gas exchange and the vital capacity of the lungs can also be measured and will often throw light on the subject in hand.

It is impossible in the short time allotted to this discussion to do more than indicate the general nature of the problem. Let me, therefore, by way of illustration, start with the consideration of the hemodynamics of thyrotoxicosis and myxedema, these being the endocrine disorders in which circulatory disturbances are the most striking.

The outstanding functional alteration in thyrotoxicosis is an increased, and in myxedema a decreased, rate of metabolism, due on the one hand to an excess, and on the other, to a shortage of the thyroid hormone, thyroxin.

The increased metabolism of tissues in the hyperthyroid individual will necessitate increased circulation, and it is the degree, manner and results of this increase that now concern us. On the ratio between metabolic rate and pulse rate there are extensive data in the literature (1, 2, 3). In general it may be said that there is a certain parallelism between the two. The results obtained by Minot and myself, which seem to be like those of other observers, show that, speaking of course in terms of averages only, for a rise of 50 per cent in metabolic rate there is a rise of about 65 per cent in the pulse rate. It was found also that the same sort of relationship held in leukemia, another disease strikingly characterized by increased metabolism. In contrast to this, it was found that when in a normal subject metabolism rate increased 50 per cent by the performance of muscular work, the pulse rate increased not more than 25 per cent (4). This is of some interest as showing that either the mechanism or the magnitude of circulatory response to metabolic rate increase may be different in health and disease.

The pulse rate, however, gives us no certain information of the actual magnitude of circulation rate increase. The amount of blood expelled by the heart per minute depends not only upon the rate of beat, but upon the amplitude of beat as well. These may vary independently. In the normal person when metabolism goes up due to the performance of muscular work, the circulation rate, that is total blood flow per unit of time, roughly parallels it, as though any increase in demand on the

part of tissues for oxygen was taken care of by a proportional increase in the supply of blood. At least this is so for milder grades of work. As work becomes heavier, the circulation rate tends to lag behind the metabolic rate, with the result that relatively more oxygen is removed from the blood in transit through the tissues. The increased blood flow with work in normal persons is accomplished partly through an increase in rate of beat, and partly through an increase in the volume expelled per systole (5).

There are but few data in existence on the blood flow in thyrotoxicosis. Field and Bock (6), at the Massachusetts General Hospital, during the past winter have made some observa-

TABLE 1
*Blood Flow at Rest**

DIAGNOSIS	CASE	BASAL METABOLIC RATE PER CENT	BLOOD FLOW LITERS PER MINUTE	PULSE RATE	OUTPUT PER SYSTOLE C.C.
Normal. .	Average		6.3	62	101
Exophthalmic goiter.	P... ..	+60	8.9	104	86
	B.	+60	14.0	93	150
	O. .	+72	11.8	102	116
	G. . .	+69	12.0	106	113
	Average	+65	11.7	101	116
Myxedema.	W	—28	2 8	48	58
	M. . .	—27	2.3	55	43
	Average	—27 5	2 55	51.5	50.5

*Field & Bock

tions in both Graves' disease and myxedema, which they have been kind enough to let me quote to you now. Their observations were made by their modification of the Fick principle of blood flow calculation. The figures obtained in normal, thyrotoxic and myxedematous subjects are shown in Table 1. While owing to the lack of sufficient knowledge of the minute volume of the circulation during rest in normal persons it is impossible to state with exactitude the per cent increase in blood flow for a given rise in basal metabolic rate in hyperthyroidism, still, on the basis of the data in Table 1, it is legitimate to draw the general conclusion that there is a distinct rise in blood flow, which at least equals, and more probably exceeds, the rise in metabolism. Somewhat similar conclusions have been reached by Davies, Meakins and Sands (7). In myxedema a reverse condi-

tion was found. That is to say, the blood flow showed an even greater retardation than the metabolism (Table 1).

It seems, therefore, that if in the normal person because of the performance of muscular work, or in the patient with Graves' disease because of excess of thyroxin, the tissues call for an increased supply of oxygen, the circulation responds to the demand adequately, that is, with an increment apparently somewhere nearly proportional to the increment in demand. The work-induced circulation increase of the normal person, however, is brought about by an increase both in pulse rate and amplitude of beat (output per systole), whereas, in that resulting from hyperthyroidism, the increased heart output seems largely to result from increased pulse rate alone, the output per systole showing a less striking tendency to rise.   .

The cause of this difference is food for thought. The suggestion is obvious that in hyperthyroidism asthenia of the myocardium, or a toxic effect of some sort, interferes with increase of amplitude of contraction. It has been fairly well established that in the case of the respiration the total amount of air pumped is controlled chemically through the pH of the blood, but that the rate and type of breathing is subject to nervous control. Since the circulation subserves the same purpose as the respiration, it is entirely possible that its method of control is the same; that is to say, as suggested by Boothby (8), the total blood flow is regulated chemically. The rate and amplitude of beat, however, to follow out the analogy, would be governed through the nervous system. Field and Bock have made two observations on the effect of atropine. Here, although the pulse rate was markedly increased, there was little or no change in blood flow, and therefore a marked diminution in output per beat. This is of some interest as being, perhaps, an instance of a purely nervous effect. It is in contrast to the result obtained in dogs by Harrison, in which it was shown that the injection of acid increases minute volume. The action of atropine, paralysis of the inhibitory fibres, is of course similar to stimulation of the sympathetic or accelerators. It is believed that some of the symptoms of exophthalmic goitre are due to excessive sympathetic activity, and it well may be that in that lies the explanation of the failure of the systolic output to increase in that dis-

ease. Whatever the cause, the result, namely the wastage of cardiac effort incident to the increase in number of systoles and the accompanying encroachment on diastole is obvious.

Arterial blood pressure is easier to determine, but less easy, perhaps, to interpret than blood flow. ·The pressure in the arteries is the resultant of two independent variables, heart output and peripheral resistance. The latter is again separated into the viscosity of the blood and the total cross section of the arteriolar bed. Read (3) has devoted particular attention to the relation between pulse rate, pulse pressure, and basal metabolism, and finds that departures of the latter from the normal, whether above or below, are closely paralleled by both pulse rate and pulse pressure. A somewhat closer correlation still was found between basal metabolism rate and a mathematical combination of pulse rate and pulse pressure.

Also of interest, but still more difficult of interpretation, are some recent observations by Thompson (10) which were started at the Boston City Hospital and now are being continued at the Massachusetts General Hospital upon the blood volume in hyper- and hypo-thyroidism made by the vital red method of Keith, Rowntree and Geraghty (11). In brief, Thompson's findings show that in hypothyroidism there tends to be a diminished, and sometimes in hyperthyroidism an increased total volume of blood plasma. Furthermore, in myxedema when thyroid is administered, volume rises, and in an exophthalmic goitre patient during an iodine remission, it fell. It would seem, in other words, as though the total quantity of available circulating medium varied with the magnitude of the demand for circulation.

Let us now, for the sake of comparison, pass for a moment to the hemodynamical action of adrenalin in normal persons. This, after thyroxin, is the endocrine hormone most definitely possessed of a calorigenic action (12). Field and Bock, however, have been able to show that, unlike thyroxin, it has an augmenting action on blood flow that far exceeds its calorigenic action. For example. in four cases of exophthalmic goitre an elevation of 65 per cent in the basal metabolism rate was productive of an elevation in blood flow approximating 85 per cent. While in a normal subject injected with 1.5 cc. of adrenalin a result-

ing 20 per cent rise in basal metabolism rate was accompanied by a 94 per cent rise in blood flow, the corresponding increments in pulse rate were 63 per cent in exophthalmic goitre and 46 per cent after adrenalin; the volumes per systole were 16 per cent in exophthalmic goitre and 33 per cent after adrenalin.

In appears, therefore, that the metabolic rate increases are accompanied by blood flow increases of varying degrees. In muscular work blood flow just parallels or falls somewhat short of metabolic increase. In hyperthyroidism blood flow parallels or somewhat exceeds metabolism, and after adrenalin injection it very markedly exceeds metabolism. In muscular work and after adrenalin there is an increase in both rate and amplitude of heart beat, while in hyperthyroidism the increase in rate is the more striking of the two.

The relative changes are indicated in Table 2, where all the factors are expressed as per cent deviations from normal rest-

TABLE 2
Blood Flow Rates*

CONDITION	SUBJECT	BASAL METABOLIC RATE PER CENT	BLOOD FLOW PER CENT	PULSE RATE PER CENT	OUTPUT PER SYSTOLE PER CENT'
Muscular work	Normal (J. H. M.)	+65	+55	+23	+25
"	"	+65	+42	+12	+30
"	"	+65	+86	+63	+16
		+20	+94	+46	+33
Myxedema........	Average (2).......	—27	—59	—17	—50

*Per cent variation from resting normal.
†From Means and Newburgh. Experiment on J. H. M. by Krogh and Lind-hard's Method. All the others are by the Field and Bock Method.
‡Variations expressed in percent above or below subjects' rates at rest in case of J. H. M. and H. F. The exophthalmic goiter and myxedema series are compared with Field and Bock's averages for normal subjects.

ing values. As stated before, what constitutes normal in the case of blood flow is but imperfectly known, so the table must be accepted as a first approximation only.

One is led to the conclusion in the case of adrenalin that there is an action directly upon the heart itself, increasing its force of beat, and that peripherally there is vasodilatation. Were there not vasodilatation with a 100 per cent increase in minute volume there would be a sharp rise in blood pressure, but there is not. In the experiment on H. F. systolic blood pressure rose comparatively slightly and diastolic fell. One also suspects that thyroxin may exert a similar action, but to a very

much less degree. With regard to adrenalin, such a conclusion does not preclude vasoconstriction in certain regions. The conclusion is simply that the sum total arteriolar effect is a widening. Constriction of skin and visceral vessels, for example, might be completely offset by dilatation of those of musculature (13). Adrenalin must likewise have had an effect upon the heart itself, for it does not seem possible to explain the great increase in minute volume by increased opportunity for arteriolar escape alone.

The effects which such hemodynamical alterations may exert must next attract our attention. A theoretical consideration of cardiac work may prove helpful. The work performed in the pumping action of the heart in the last analysis comes down to the total amount pumped and the pressure against which it is pumped. Thus, in a normal man at rest if the minute volume is six liters and the mean blood pressure is 100 mms. of Hg (which is equivalent to 1.28 meters of blood) the work is $6 \times 1.28 = 7.68$ kilogram meters per minute. In Table 3 this is contrasted with certain pathologic states. The values are assumed, but in view of the known facts, the values as given are reasonable. Either a state of hyperthyroidism elevating the basal metabolic rate to plus 65 per cent, or an adrenalin effect elevating it 200 per cent, will double the blood flow without great change in mean blood pressure, and, consequently will double cardiac work. But so, too, would an arterial hypertension with a mean pressure of 200 and no acceleration of blood flow. In marked contrast is the state of affairs in myxedema in which the work of the heart must be greatly reduced.

In either hypertension or hyperthyroidism there will be, even at rest, a marked increase in the task the heart must perform, and, consequently in each cardiac hypertrophy and later fatigue and perhaps failure. Greater degrees of hypertrophy are seen in chronic hypertension, but this may be because hypertension lasts longer than an hyperthyroidism. Or the heart may fail sooner in hyperthyroidism because, though the extra load may be no For exhan i in hypertension, the more rapid rate gives less of 65 per. White and Sprague (14) have recently made some an elevation of length of systole in normal and thyrotoxic in a normare obj show that while in a person with a pulse rate

of 60 the total length of systole per minute may be but 24 seconds, in a thyrotoxic person with a pulse rate of 130 it may reach 35 seconds. Such a shortening in total diastole, if long continued, might alone greatly increase cardiac fatigue.

Whether the thyroid hormone in toxic goitre also exerts an actual toxic effect upon the heart is a matter of dispute. The work of Goodpasture (15) indicates that even if it does not do so directly it at least predisposes the heart muscle to destruction by other toxins.

The actual circulatory symptoms and signs of hyperthyroidism and myxedema are sufficiently familiar to make enumeration here unnecessary. The points that I should like to emphasize are that those of hyperthyroidism are understandable on the basis of the known morbid physiology; that is, rapid metabolism and blood flow and a certain amount of arteriolar dilatation, together with the direct cardiac resultants of long continued overwork and hurry, and finally fatigue and failure. The

TABLE 3
*Cardiac Work**

CONDITION	BASAL METABOLIC RATE PER CENT	BLOOD FLOW LITERS PER MINUTE	MEAN BLOOD PRESSURE MMS.	HEART WORK KGM. PER MINUTE
Normal.	0	6	100	7
Hyperthyroid	+65	12	100	14
Hypertensive.	0	6	200	14
Adrenalin injected .	+20	12	100	14
Hypothyroid. .	−30	3	• 100	3.5

*Theoretical.

symptoms and signs of myxedema are in the main the converse and due to converse conditions.**

Of circulatory disturbances in other diseases of the endocrine glands I shall say nothing, for until their hemodynamics are worked out interpretation of signs and symptoms is largely guess work. I may simply mention in closing that in all, doubtless, there are circulatory abnormalities. I need but cite the hypotension of Addison's Disease, and the fact that from the pituitary is obtained a substance for short periods highly pressor in action. The gonads, too, probably have their circulatory action; witness the circulatory disturbances of the menopause. But the

** The myxedema heart recently reported by Fahr (16) is of great interest, but difficult of interpretation.

nature of the mechanism of these is not sufficiently understood
to warrant discussion at this time.

BIBLIOGRAPHY

1. Sturgis, C. C., & Tompkins, E. H.: A study of the correlation of the basal metabolism and pulse rate in patients with hyperthyroidism. Arch. Int. Med. (Chicago), 1920, **26**, 467.
2. Minot, G. R., & Means, J. H: The metabolism-pulse ratio in exophthalmic goiter and in leukemia. Arch. Int. Med. (Chicago), 1924, **33**, 576.
3. Read, J. M.: Basal pulse rate and pulse pressure changes accompanying variations in the basal metabolic rate. Arch. Int. Med. (Chicago), 1924, **34**, 553.
4. Means, J. H., & Newburgh, L. H.: Studies of the blood flow by the method of Krogh and Lindhard. Tr. Ass. Am. Physicians (Phila.), 1915.
   Ibid.: Effect of Caffeine on the blood flow in normal human subjects. J. Pharmacol. & Exper. Therap. (Balt.), 1915, **7**, 449.
5. Means, J. H.: Dyspnoea. Medicine, 1924, **3**, 309.
6. Field, H., Jr., Bock, A. V., Gildea, E. F., & Lathrop, F. L.: The rate of the circulation in normal resting individuals. J. Clin. Inves., 1924, **1**, 65.
   Field, H., Jr., & Bock, A. V.: Action of adrenalin chloride on circulation rate in man. Proc. Am. Soc. Clin. Inves., 1925.
7. Davies, H. W., Meakins, J., & Sands, J. The blood gases and circulation rate in hyperthyroidism. Heart (Lond.), 1924, **11**, 299.
8. Boothby, W. M.: A determination of the circulation rate in man at rest and at work. Am. J. Physiol. (Balt.), 1915, **37**, 383.
9. Harrison, T. R.: The rôle of H-ion concentration in regulating the circulatory minute volume. Paper read at meeting of the Cosmopolitan Medical Club, Johns Hopkins Hospital, Feb. 14, 1925.
10. Thompson, W. O.: Personal communication.
11. Keith, N. M., Rowntree, L. G., & Geraghty, J. T.: A method for the determination of plasma and blood volume. Arch. Int. Med. (Chicago), 1915, **16**, 547.
12. Boothby, W. M., & Sandiford, I.: A quantitative estimate of the catalytic power of adrenalin and thyroxin as calorigenic agents. Proc. Am. Biochem. Soc., Dec., 1923.
13. Hoskins, R. G.: The relation of the adrenals to the circulation. Physiol. Reviews (Balt.), 1922, **2**, 343.
14. White, P. D., & Sprague, H. B.: Personal communication.
15. Goodpasture, E. W.: Myocardial necrosis in hyperthyroidism. J. Am. M. Ass. (Chicago), 1921, **76**, 1545.
16. Fahr, G.: Myxedema heart. J. Am. M. Ass. (Chicago), 1925, **84**, 345.

PSYCHICAL DISTURBANCES IN THE DISEASES OF THE GLANDS OF INTERNAL SECRETION[*]

C. MACFIE CAMPBELL
BOSTON

The relation of disease of the glands of internal secretion to mental disturbance is no simple problem. For its solution the experimental method is available to but a very limited extent, and we have to take the material supplied by nature, which has little respect for the conditions of an accurately controlled experiment. Before we correlate mental disturbance with endocrine disorder we must have in each case some reasonable degree of certainty as to the nature of the endocrine disorder and a fairly precise analysis of the mental disturbance; even when we are ready to associate in close union the endocrine disorder and the mental symptoms, we must not be surprised should the statistician forbid the banns.

The internist is familiar with the difficulty of establishing in each individual case the exact nature of the endocrine disorder, which expresses itself in the physical structure, the physical symptoms and the reactions to special tests; to the psychiatrist it is not necessary to emphasize the difficulty of giving its due weight to each of the numerous factors, which are liable in the individual case to contribute something to the disturbance of the patient's social behavior, his beliefs, his emotional balance.

In view of these difficulties it is not to be wondered at that so little progress has been made in this special field since Cushing's (1) appeal for co-operative investigation at the opening of the Phipps Psychiatric Clinic in 1913, and I do not know that I have anything substantial to add to the principles laid down in that address.

The first step to be taken is the careful accumulation of cases with unequivocal evidence of a well-defined endocrine disorder. Such cases are usually observed in a surgical or medical service, where anomalies of structure and of metabolism are

201

studied intensively, while mental disturbances are apt to receive summary mention.

In "An Autograph History of a Case of Addison's Disease" by A. L. Muirhead (2) we find little mention of the personal factors in the total reaction. Even though the author had given a more detailed account of such personal reactions, it might have been difficult to disentangle them from the general tissue of the personality, woven as the latter is from native endowment and individual destiny, as well as from the single coarse strands of organic function, and after disentangling them to correlate them with the disturbed function of the adrenal glands. In early life Dr. Muirhead suffered from indigestion: "It produced a feeling of weariness, drowsiness and depression that often interfered with his studies. This condition continued, in varying degree, for a good many years and at times caused depression, both physical and mental, almost as marked as Addison's disease does at the present time."

The depression which was observed after the definite development of Addison's disease might be interpreted as symptomatic of disordered function of the adrenal glands, or on the other hand it might be regarded as the reaction to the physical disorder of a personality, whose latent depressive trend had already been elicited by the digestive trouble in the early twenties. Such a depression might therefore be deeply rooted in the constitution of the individual. Without a careful review of the heredity of the patient, and of his early development, the interpretation of the depression as the direct expression of the disordered function of the adrenal glands would be rash. It is true

that in the fan
correlated with
may be an out
shown among
gland, and by
We are, howeve
tion" into a glar
The difficul
... disor...
... ...

ily, as in the patient, traits of personality may be
 glandular anomalies. A glandular inferiority
 standing feature in a family stock as has been
 others by Barrett (3) in relation to the thyroid
 Cushing (4) in the case of the pituitary gland.
 r, at present seldom able to translate "constitu-
 dular formula.
 ty of correlation of mental disturbances with
 ers is further exemplified by Leonard Mark's
 ysis of his own acromegalic experience, re-
 g in his 1913 address. In this account Dr.

Mark tells in detail of his various distressing symptoms: "When I am at my worst I still seem to be master of all my mental faculties, but lose the inclination to make best use of them. There is some mental depression, but it is overbalanced by the strong feeling that if I can only remain perfectly still for a little while the condition will pass off and I shall be all right." This mental condition is very different from other conditions which the psychiatrist is accustomed to group together under the term "depression," conditions in which there is a feeling of lonesomeness, lack of ambition and hopelessness and in which one sees no preservation of that central confident personality, which looks upon the distressing feelings as something outside of itself. In such conditions the citadel of the personality itself is in the hands of the foe, while in the experience of Dr. Mark the enemy seems still to be without the walls. Had not Dr. Mark had such a stout heart the central personality itself might have surrendered. As a matter of fact Dr. Mark admits the transitory development of such a depressive state when he learns the nature of his disorder. "I must confess that the first effect of the knowledge that I was suffering from such a malady had a most depressing effect upon me and for several days I went about feeling profoundly miserable. The first taste of the fruits of knowledge was indeed bitter; I felt that I should soon grow rapidly worse and dreaded what might be in store for me. I was also exceedingly annoyed with myself for not having made the discovery sooner and felt I must be branded as an ignoramus for not knowing more about acromegaly." These emotional reactions to the complex situation can apparently be definitely separated in the case of Dr. Mark from the previous symptoms, which represent a different type of mental depression of somewhat simpler nature, closely related to feelings of general discomfort and fatigue. It is important in correlating endocrine disorders with mental disturbances to keep in mind clearly the distinction outlined above. It is probable that in the case of Dr. Mark the type of mental depression associated with the fatigue and discomfort was closely related to the pituitary disorder, while the type of depression which, for a short time, overwhelmed him after learning the nature of his disorder may have had no specific relation to the pituitary disorder but was dependent upon

much more subtle and complex functions which are included in the general term personality. It is not suggested that the personality is a metaphysical entity or entelechy apart from the component organs and systems of the body; the personality is a term which includes very complex reactions to which no doubt ·the pituitary gland contributes its quota like every other component of the body, but one can make a distinction between the reaction of the whole individual to the knowledge that he has an incurable disease of the pituitary gland, and certain distressing feelings recognized by the personality to be as extraneous as feelings of discomfort and fatigue. In disorders of the other glands of internal secretion we meet the same problem. In diabetes we have to consider not only the hormonic influence of the gland but the reaction of the individual patient to the knowledge that he has a serious disease. In the case of a woman· who has had double ovariotomy we have to consider not only the endocrine influence on mood and thought and behavior but also the reaction of the individual woman to the fact that she has been sterilized and her whole career has been seriously altered.

Further reference may be made to the interesting case of Dr. Mark. He devotes one chapter to describing various noises in the head—a seething sound, fizzing sounds, a buzzing sound. At the same time tunes were continually running in his head in a not unpleasant way. His symptoms would be more relieved by a sonata of Beethoven than by a dose of antipyrin. The former would soon put him right "and in less than twenty minutes I should be feeling quite comfortable and the head trouble would have been charmed away." In these symptoms, as in the reaction of the total personality to the situation of his disease, we may perhaps see a very large contribution from the individuality of the patient, and must be on our guard against correlating them too directly with the disorder of the pituitary gland. Patients vary not only in their total personality, in their temperament and dominating mood, but also in their sensory endowment, and the total clinical picture is liable to bear the very definite imprint of the special endowment of the individual.

Owing to the kindness of Dr. Cushing it has been possible for me to see a series of cases of dyspituitarism, the larger number of whom were suffering from acromegaly. I have been im-

pressed by the comparatively slight modification of what one might call the central personality and by the fact that the mental symptoms touch so little the emotional ground work of the personality; one meets variation in output of energy and various slight changes of mood, either expressive of the special constitution or in reaction to the special life situation which the disease has created.

A young woman of thirty-two, always slightly self-conscious, since the development of her acromegaly had shown a natural sensitiveness to the change in her physical condition and a corresponding degree of seclusiveness. She showed no definite depression and was less inclined to have blue spells than during her girlhood. She still enjoyed to a normal degree musical and intellectual opportunities. She was subject to periods during which she would feel that she had less initiative and had to urge herself to do things. She formulated the influence of the disease on her mental state as "a simplifying—I don't care to be as analytical as before, I am quite willing to let things take their course, to drift along." In such a case we are reminded of some of the symptoms of Dr. Mark, of his feeling of fatigue, his desire to keep still, his disinclination to make the best use of his mental faculties. and as in the case of Dr. Mark the symptoms come and go. There are times when she has as much energy and enthusiasm as ever. She feels no slowness in her thought even when she is slow in her movements.

An Armenian of forty-seven with acromegaly would have bad dreams. Later he developed episodes during which his mind passed into a peculiar condition, although he was not unconscious. A five-minute nap would put him all right. In this patient one saw no alteration of the fundamental mood—he was placid and not depressed; he felt that his memory was not so good and that concentration was a little more difficult.

A rather simple Irishman of fifty-six with chronic myocarditis seemed to take his acromegaly in the most matter-of-fact way.

A woman of forty-eight with acromegaly had shown progressive blindness; at first she had cried a little about this handicap, but had shown no other depression At times she would have a feeling of being afraid to be alone. She had periods when she would be slower in her activity than usual. She complained of "slowing up of cerebration" and said that she was very forgetful. In this case we see a patient reacting courageously to her blindness and to the slight difficulty of her thought processes. Morbid fear may have many sources and one would hesitate to associate it directly with the dyspituitarism.

A steamfitter of forty-four with acromegaly complained of his head occasionally becoming confused so that he gave up driving his car on Sunday. Ten years previously he had become more irritable, but after a year he improved in temper owing to his wife's admonitions. At the time of examination one saw remarkably little modification of the personality; he reacted to the situation in a very matter-of-fact way; his only complaint in regard to mental functions was that it took him a little longer to grasp things.

A woman of forty-eight with acromegaly showed a remarkable preservation of normal interests and a very even disposition, although suffering from headache and progressive weakness. There was a certain slowness in her reactions and she was somewhat depressed over the fact that so little could be done for her severe headaches.

In the above cases of dyspituitarism of the acromegalic type one notices practically no primary disorder of mood, no changed attitude towards life, variable loss of energy and initiative, occasional complaints of lack of concentration or forgetfulness.

If one turn from the acromegalic type of dyspituitarism to the large group of cases where hypopituitarism is suspected one has a most complicated group of cases to deal with; in such instances the exact rôle of the pituitary gland may be somewhat obscure and the total analysis of the personality forms an important part of the investigation. A very partial view of the situation is apt to be obtained by the individual worker, owing to the circumstances which determine the material which comes under his observation. The psychiatrist to whom patients are brought on account of lack of intelligence or difficulty of behavior will tend to overestimate the frequency of such defects in patients with hypopituitarism. In cases presenting Froehlich's adiposogenital dystrophy, mental retardation and anomalies of character and behavior are frequently observed by the psychiatrist; on the other hand, these mental anomalies show little of specific nature so far as I am aware and similar personal traits may be observed in other types of constitutional inferiority. It is possible that in patients of the Froehlich type, with mental anomalies, the mental and physical disturbances may be parallel manifestations of some developmental flaw, and the mental disturbances need not be secondary to the endocrine disturbance.

An interesting type of dyspituitarism is furnished by certain children who are physically very immature, but who may be bright and intelligent, even precocious.

An example is a boy of fourteen with the physical development of a boy of about eight. His mental age as determined by standard intelligence tests is that of the average boy of seventeen. His conversation has the formal precision of the youthful Macaulay, answering the kind inquiry as to his toothache with: "I thank you, madam, the agony has abated." The patient occasionally plays ball: "I take advantage if allowed the opportunity." His attitude towards girls is formulated as follows: "There was a certain lady back home who had something of an attraction for me." This patient of Dr. Cushing recalls the case he has reported of the girl nine years of age who "behaved like a prim little old lady."

The field of thyroid disorders is perhaps less complicated than that of pituitary disorders and the interpretation of the

cases is not complicated by the dual nature of the gland. The presence of mental disturbances in thyroid disorders is very familiar but the subject requires ⸌a great deal of further study. Superficial resemblances are often made the basis of seductive hypotheses. The contrast between the energetic activity of the case of hyperthyroidism and the slowness of the myxedematous patient has led to the facile suggestion that in the alternations of elation and depression in the manic-depressive condition we have the expression of a recurrent thyroid disturbance. The close scrutiny of the actual nature of the disturbance in definite thyroid disorders makes one hesitate to accept the analogy.

A woman* in the forties had for several years since the death of her husband been very nervous. Two years before thyroidectomy she would wake up at night with the feeling of someone in the room; she would be afraid to draw a breath "lest they hear me." She would then bolt for the children's room and get them to search the house. Even before her husband had died she was too nervous to live on the first floor, she would be unable to sleep until he came in. For some time before thyroidectomy she showed the restless energy and lack of placidity characteristic of hyperthyroidism: "It seemed I had to be doing something all the time—I would say, I'll sit down, but I had to be up again." She found it difficult to sit and read the paper; she could not concentrate if anyone were talking. Before correlating the emotional state of the patient directly with the hyperthyroidism it is well to note that at the age of twenty, after three years in the United States, she had a period during which she was "all tired out, had no ambition; I felt a little nervous; I would jump if the bell rang." It is possible that such an episode has to be formulated in terms of the total constitution of the individual and not in terms of merely one gland, and in her later mental symptoms we have to weigh the contribution of her special constitution as well as the influence of the hyperthyroidism. Certain episodes in her life may also have tended to reinforce a tendency to fear, for her husband was a policeman and had been twice seriously assaulted.

A married woman of twenty-seven had been quite fearless previous to her mother's death, when she was twenty-four. She was active, ambitious, irritable, domineering. With the development of definite hyperthyroidism, she showed in her mood an accentuation of her previous traits. She was more domineering and sensitive and had less control of her reactions. There was no special feeling of depression. The slight restrictions of hospital life led to tantrums, tears, and protests. She felt restless, and before admission to the hospital had carried on an unnecessarily full programme of domestic and social activities. Concentration was difficult; she would force herself to read one page ten times. Her sleep was disturbed as she felt so fidgety. The eager talkative condition of such a patient has a superficial similarity to the excited phase of a manic-depressive patient, but there are also points of dissimilarity. The mood cannot at once be identified with that of the manic patient, although the

latter may vary from definite euphoria to marked irritability. The over-activity of the manic patient is apt to be futile and exuberant and has frequently lost the normal purposive quality, which is retained in the case of hyperthyroidism. The patient referred to above was very talkative, alert, commenting on a variety of topics. There was no tendency, however, to pun or to rhyme; in the talk of the patient, as in her behaviour, the purposive or adaptive quality was still retained, while in the manic excitement it is seriously diminished if not altogether lost. The family history of the patient was of some interest: her paternal grandmother, her father and three out of the five siblings having very hasty tempers; the mother was subject to recurrent spells of depression. The question may be raised as to the rôle played by the thyroid gland in the constitutional explosiveness of her relatives and as to how far her own early eager, energetic, ambitious temperament was largely conditioned by her thyroid endowment.

In the above case the emphasis has been laid upon the restless activity of the patient, her mood, her inability to concentrate, her original constitution. One may refer to these factors in a few other cases of hyperthyroidism. One woman who has just remarried admits that she works on her nerves. She wants to do gymnastics, dancing, etc. The wife of the policeman referred to above "had to be doing something all the time." In two other cases the over-activity was sadly complicated by constant nagging and scolding. A woman of 32 frankly admitted, "I was going it all the time with my tongue; I could not keep still." Another patient of 59 had to be continually checked in her loquacity by her daughters, "Keep quiet, mother, you have said enough." It is not to be wondered at that in the home of the hyperthyroid woman, marital complications are not infrequent, even with a long-suffering husband.

The mood of the above patients was varied. The young woman of 27, referred to above, although irritable and with tantrums, claimed that she was quite happy. She appeared to be "keyed up"; the difference between her mood and that of the euphoric manic patient might be compared to the difference between an individual stimulated with strychnine and one who is exuberant from champagne. For a satisfactory analysis the mood must be studied in relation to the family history, and the early temperament, as well as in relation to the thyroid disorder.

As to the intellectual functions several patients mentioned difficulty in concentration and impairment of memory.

Most physicians are familiar with the general mental reaction of the myxedematous patient—the slowness, the apparent intellectual dullness, the occasional depression, the impairment

of memory. It is possible that one accepts too readily the dullness of the patient as evidence of a depressed mood.

A girl of 18 with mild hypothyroidism admitted no depression at all. A severe case of myxedema showed the gradual onset of sluggishness, day-dreaming, loss of interest: "The outside did not concern me—I was like a dead one, that's all—I·had a blue spell, tears were running down like rain, I wondered why it was the way I felt." This patient when seen later in an advanced stage of myxedema said that she was not depressed, but that she was in good spirits. However, at times she would be seen crying quietly, distressed at her own condition, the seriousness of which she apparently appreciated. She was much more alert than her slow talk would indicate. She had good insight into the thought difficulty: "My thinking is not good—I don't want to think—it bothers me to think too much. There was a time when my mind was just traveling, now it is at rest." In connection with this last remark, it is interesting to note that the patient had previously been an ambitious, energetic woman, enjoying making a speech to her family circle at Thanksgiving and at Christmas time.

Another patient, a woman of forty-nine, made no reference to any depression, but emphasized the progressive loss of memory. As a waitress she had been accustomed to wait on five tables, but finally was unable to remember the order of a single person. She later kept house for her son, but was considered extremely lazy, letting her work alone until it was absolutely necessary to do it. There seemed to be little change of mood. After suitable treatment, the laziness disappeared and she felt "like a bird."

The importance of the sexual instinct in relation to mental and nervous disorders has in the past two decades received new emphasis. The analysis has been specially detailed at the psychological level, while accurate information as to the rôle played by the hormonic influence of the gonads upon the various mental functions is still far from clear. Even in thyroid and pituitary disorders the rôle played by the gonads may be far from negligible, and it is not easy to disentangle the specific contribution of the disordered action of the gonads to a pluriglandular syndrome. Such being the case, it is still more difficult to trace the relation of the hormonic influence of the gonads to mental symptoms or traits of personality, when one has to consider as well racial characteristics, individual temperament and life situation. It is interesting to study the characteristics of the Skopts, a Russian sect in which castration of the men and mutilation of the women are an essential religious rite, but the traits of character of the members of such a sect are determined by too complex factors to make such material of much value in the present discussion. Analysis of the mental traits of eunuchs and eunuchoids is also a matter of considerable difficulty. There should be a careful study of the mental disturbances in patients

in whom the gonads have been removed by operation or through trauma. I have not personally had the opportunity of studying such clinical material. The difficulty of coming to any sound conclusions even in regard to certain simple reactions is shown by the varying statements recorded in the literature. Pfister (6) calls attention to the fact that statements with regard to the continuation of sexual desire after double ovariotomy are very conflicting. In his cases the influence on the libido was very variable. The mood of about one-half of his patients after double ovariotomy was one of depression and irritability, while about one-third of the subjects felt more cheerful. The mental changes after the operation cannot be easily correlated with the variation in the hormonic situation, but are also determined by the general change in the physical well-being of the patient, by the realization of the different life-situation created by sterilization, and by the special temperament of the patient. Fischer (7) reports three cases of young men with traumatic castration. A soldier of 28, one year after the trauma, developed various attacks, first of all like asthma, later like fainting, and finally convulsive attacks in 1920; complete impotence, loss of sexual desire, irritability, suspicion, outbursts of wrath, sensitiveness to sound, periods of depression with attempts at suicide, ideas of reference. He had good insight into his change of character. A second patient, a man of 27 of cycloid temperament, is said to have developed a schizoid temperament. In a third case, the fact that the patient was blown up makes the detailed correlation of the later symptoms with the castration still more difficult. The cases utilized by Fischer indicate how unsatisfactory the available clinical material is for the solution of the problem that interests us.

With regard to the pancreas, a large amount of clinical material is available. In a small series of diabetics whom I have had the opportunity of interviewing, I have been impressed by the bright and cheerful attitude of the patients. A diabetic woman of 67, when she was asked if she were depressed, said, ''Not a bit, it did not bother me; we have to get something to kill us.'' Another diabetic woman of 47 said, ''I don't believe in feeling blue; it don't get you anywhere.'' Such was the general attitude of this small group of diabetics, all of whom were over 40

years of age. One patient had been rather blue and depressed, but this was not surprising in view of the fact that her husband had wanted to kill everybody and had been sent to a hospital for the insane. Another patient had been mildly depressed and unable to concentrate, but this was apparently during a period of considerable weakness.

It should not be difficult to ascertain whether in the diabetic there is a tendency to any specific disturbance of mood or thought or conduct, and whether in the psychoses incident to the disease there are features different from those met with in psychoses associated with exhaustion of other origin.

The psychiatrist sees in many patients with psychoses some evidence of endocrine anomaly; the internist sees in his patients with endocrinopathy the not infrequent development of a psychosis. The analysis of a psychosis, and the due appreciation of the various elements in the etiological constellation are matters of some difficulty; before they can be profitably undertaken we require much more light on the simpler problems discussed in this communication.

The psychiatrist looks eagerly to the physiologist and to the internist for guidance in this matter; the latter will furnish help when he renews his interest in the personality and remembers that mood, mental attitude, belief, conduct are factors in adaptation, open to objective biological study, of as much importance as the simpler metabolic machinery. The psychiatrist finds that the break-down of a patient in face of a definite environmental stress is due to the inadequate resistance of the individual, to the temperament or constitution as modified by its individual experiences. He can describe and analyze this constitution, can try with Kretschmer (8) to correlate it with physical habitus, but he cannot easily localize it or express it in the definite bio-chemical, immunological or endocrine formulae which the laboratory mind finds so satisfactory.

In his inability to specify exactly where is localized man's resistance to bereavement, thwarted career, disappointed affection, social inferiority, and to give a bio-chemical formula for it, the psychiatrist is not in a very different situation from the internist, who may be puzzled to localize the mechanism of de-

fense against the tubercle bacillus and to express it in other than complex immunological terms.

The internist steadily tries to make more specific these latter terms, to reduce them to simpler components; so the psy-chiatrist aims to make more precise the factors which enter into the constitutional defenses of the personality against the environmental stress and among these factors he knows that the endocrine glands play an extremely important rôle. If I have ventured as a psychiatrist to address you on a topic so complicated as that of the present communication, with so little to offer and with such slight contact with the necessary clinical material, it is in the hope that you will answer the appeal, "Come over into Macedonia, and help us."

BIBLIOGRAPHY

1. Cushing, H · Psychic disturbances associated with disorders of the ductless glands Am. J Insan (Utica), 1914, 69, 965-990
2. Muirhead, A. L An autograph history of a case of Addison's disease. J. Am. M. Ass (Chicago), 1921, 76, 652-653
3. Barrett, A M Hereditary occurrence of hypothyroidism with dys-. trophies of the nails and hair. Arch. Neurol & Psychiat. (Chicago), 1919, 2, 628-637
4. Cushing, Harvey The pituitary body and its disorders, clinical states produced by disorders of the hypophysis cerebri. J. B. Lippincott Co , Phila & Lond , 1912, 351 pp , front, roy. 8°.
5. Mark, Leonard Acromegaly, a personal experience. Balière, Tindall & Cox, Lond , 1912, 168 pp , 11 pl , 8°
6. Pfister, A Die Wirkung der Kastration auf den weiblichen Organismus. Arch f Gynaek (Berl), 1898, 56, 583-634.
7. Fischer Die Wirkung der Kastration auf die Psyche. Ztschr. f. d. ges Neurol u Psychiat (Berl u Leipz).
8. Kretschmer Korperbau und Charakter. Julius Springer, 1922, Berl

INTERPRETATION OF DISTURBANCES IN METAB-
OLISM DUE TO THE GLANDS OF INTERNAL
SECRETION*

GRAHAM LUSK

From the Department of Physiology, Cornell University
Medical College
NEW YORK CITY

Meltzer was a convinced believer in the doctrine that most
of the great advances in physiology have come from practi-
tioners of medicine. In the field of internal secretions Addison
(1860), Graves (1853), Gull (1890), Horsley (1916), Murray,
Friedrich Müller and Kocher were the pioneers. That Banting,
possessed of an idea, left the practice of medicine and inspired
the discovery of insulin shows that the breed is not extinct.
The subject matter of the internal secretions has in the course
of its development become so complex that much has been written
of it that is of purely imaginative character.

Many years ago Lewellys F. Barker wrote some editorials
entitled "The Truth and Poetry of Uric Acid." Clinicians have
stopped writing poetry about uric acid, for the field has been
greatly extended. The appearance of a vast amount of poetry
on the subject of endocrinology has in its turn filled the medical
journals. One of the earliest themes I can recollect declared
that β-granules of glycogen were carried from the livers to the
heart by the blood and there in the heart, in conjunction with
epinephrin, became the cause of the heart beat. I refer to this
as indicative of the poetical method in science, because neither
before nor since have the imaginative β-granules of glycogen
been mentioned in the literature, nor did the writer of the poem
vouchsafe to indicate how he had discovered them.

We all owe much to von Noorden, who came as a *Meister-
singer* of old, with a melodious triangle—pancreas, thyroid, adre-
nal. He sang that epinephrin stimulated the thyroid, increas-
ing protein metabolism, which it does not, and that epinephrin
inhibited the pancreas and prevented the oxidation of sugar,

---

*Read before the Association for the Study of Internal Secretions,
Ninth Annual Meeting, Atlantic City, May 26, 1925.

213

which it does not, and that it caused the production of sugar from fat in the liver, which it does not. Also that the removal of the thyroid gland prevented the increase in protein metabolism in diabetes, which is actually true. Of recent date is the perfectly good theory of a very good man, Epstein (1) that trypsin destroys insulin in diabetes. I hailed this with delight, for it explained why, after giving meat to a diabetic free from urinary sugar, profound diabetes could be induced. Apparently, the meat diet increased the production of pancreatic trypsin and diabetes ensued. But alas, Collens (2), a young practitioner of medicine working in spare moments in my laboratory, has shown that the experimental evidence was inconclusive and that the results found were due to an adventitious influence upon the liver. The evidence offered is insufficient.

The heat production in a normal resting mammal is a constant, called the "basal metabolism," and in mammalia it is the same per square meter of body surface. When food is given the heat production rises above the level of the basal metabolism and this increase in the heat production is called the "specific dynamic action" of the particular food administered. During one and the same week I have read or heard discussed papers attributing the specific dynamic action to (1) thyroid; (2) adrenals; (3) sex glands; (4) hypophysis. When one considers this list one must again revert to poetry,

> "Here's a pretty mess,.
> Here's a state of things."

I do not wish to be hypocritical, but I do wish to say just one or two things based on personal experience. In the first place, *if the dog moves,* its metabolism is not *basal metabolism.* In the second place constant confinement in a cage may reduce the basal metabolism of a dog 20 per cent. In the third place, the height of the basal metabolism depends on the plane of protein nutrition. There are all kinds of experiments on all kinds of animals which will not stand the test of a strict analysis in the light of these criteria. As far as dogs are concerned, if we know their weights. we have sufficient data to tell whether experiments reported from other laboratories are worth while or not. As far as our laboratory is concerned, we believe that we have trustworthy experimental data upon the basal metabolism

of dogs and young hogs. We feel that some good work may have been done upon cats. We are doubtful about rabbits, which are excitable little beasts, and we look askance at results obtained on chickens, pigeons, rats* and mice.

For example, Deuel's (3) work has shown conclusively that the presence or absence of vitamin B is without influence upon the basal metabolism of dogs, although Abderhalden (4), working with pigeons, found vitamin B a necessity for maintaining normal metabolism. It is easier to ascribe these latter results to an impossible technique than to a difference in the behavior of the tissue of dogs and of pigeons.

The difficulties of the subject of even simple problems related to the internal secretions are very great, as may be seen from the prolonged dispute between Cannon and Stewart, now settled by the experiments of Anrep and Daly (5), which confirm Cannon's contention that asphyxia increases the output of epinephrin from the suprarenal glands. There are excellent reviews of the literature on the subject of the respiratory metabolism as influenced by the internal secretions, such as that of Aub (6), so that I may be pardoned if today I indicate only a few salient facts.

THE THYROID

. It was Friedrich Müller who first pointed out that, notwithstanding a large food intake, a patient suffering from exophthalmic goiter could not maintain his weight, and it was Magnus-Levy who carried the technically difficult respiration apparatus of Zuntz to the bedside and there proved the existence of a greatly increased metabolism in this disease. Du Bois was the first to establish accurate standards of basal metabolism for normal human beings. He differentiated between mild, severe and very severe cases of exophthalmic goiter as having metabolisms which were respectively 25, 50 and 75 per cent above that of the normal individual. This useful classification has led to the widespread employment of respiration apparatus in the clinic, though too often the value of the apparatus as an interpreter in other diseases has been ridiculously overestimated.

The discovery of thyroxin by Kendall is one of the highest significance. His writings do not reveal his methods, but the

---

*Asher's method with sleeping rats is reported to be reliable.

physiological effect of thyroxin is like that of the thyroid gland, relieving cretinism and myxedema. Thus, when 16 mg. of thyroxin were administered by Plummer and Boothby to a myxedematous and apparently thyroidless patient with a metabolism 30 per cent below normal, the metabolism gradually rose to a maximum and then gradually fell to the original level after a period of about six weeks. The 16 mg. of thyroxin caused a production of 16,125 calories above the quantity this patient would otherwise have produced. This is the equivalent of the heat liberated in the oxidation of 4.25 kg. of glucose. In the words of Plummer, thyroxin is "a catalyst that accelerates the formation of a quantum of potential energy in the cells of the organism." A milligram may be responsible for an increase in metabolism equal to the oxidation of 267 gm. of glucose, or 267,000 times the weight of the catalyst. Thyroxin is the most powerful agent known for inducing increased metabolism.

Kendall (7) states that the acceleration of oxidation in the animal organism by thyroxin is due to the fact that it is an active hydrogen acceptor and that the degree of stimulation is due to the oxidizing potential of this hydrogen acceptor.

In exophthalmic goiter Plummer (8) has observed that administration of iodine in the form of Lugol's solution may greatly reduce the nervous symptoms and prevent the further development of eye symptoms. He believes that two substances are active here, thyroxin and a toxic product, which latter is neutralized in the presence of iodine, which renders it innocuous. The basal metabolism falls under this procedure and the danger of operation on the thyroid is greatly reduced.

It is of great interest that in exophthalmic goiter the human machine is inefficient in the accomplishment of mechanical work. Boothby and Sandiford (9) have shown that twice the number of calories are required to accomplish a given amount of work as are normally needed.

This work of the Mayo Clinic is of a kind which, had it been produced in Germany a decade ago, would have been hailed as a triumph of German medicine. To those of us who never questioned American intellectual ability to equal the German effort it comes, not as a surprise, but as a cause for congratulation that this co-operative work of clinician, chemist and physi-

ologist should have been conducted by Americans who were born and wholly educated in this country.

It is reported from Vienna by Liebesny (10) that thymus, administered with potassium iodide, greatly reduces metabolism in hyperthyroidism. Thymus given alone is inactive, and potassium iodide alone increases the basal metabolism. These investigations might be repeated under careful control.

Recent experiments by Lauter and Jenke (11), who worked in the medical clinic of Friedrich Müller in Munich, show that, if sufficient carbohydrate be given in a case of severe exophthalmic goiter, there is no greater amount of protein metabolism than in a normal individual. Hence, thyroxin does not attack organized tissue.

An important paper by Aub, Bright and Uridil (12) shows that thyroxin acts upon the basal metabolism of cats anesthetized with urethane just as powerfully after adrenalectomy as before operation. *The adrenals are therefore not essential to the maintenance of the high metabolism induced by thyroxin.* The anesthetic prevented all muscle tremors.

THE ACTION OF EPINEPHRIN

In Addison's disease the heat production has been found to be 15 to 30 per cent below the normal. The last was a patient of Dr. L. G. Rowntree reported by Muirhead (13). Aub, Forman and Bright (14) have described how cats, forty-eight hours after the removal of the adrenal glands, manifest a reduction in metabolism of 25 per cent. Aub, Bright and Forman (15) likewise show that this fall in metabolism takes place after removing the thyroid, and hence *the thyroid has nothing to do with the reaction.* They also introduced epinephrin at the usual physiological rate of its production into thyroidectomized dogs and found an increase in metabolism. They conclude that epinephrin effects a quick, almost immediate response and thyroxin a slower one, a finding also emphasized by Boothby.

Boothby and Sandiford (16) have published an illuminating paper on the subject of calorigenic action of epinephrin. They found that the increased metabolism resulting from the administration of epinephrin in man could not be interpreted as the result of carbohydrate plethora induced by the drug. After giving 100 gm. of glucose the blood sugar doubled, and after

giving 0.5 mg. epinephrin it rose only one-third above its original level, whereas the heat production rose 9 per cent after giving glucose and 20 per cent after epinephrin. Furthermore, in a case of complete diabetes complicated with exophthalmic goiter with a basal metabolism of plus 80, epinephrin given subcutaneously increased the basal metabolism to plus 149 without any oxidation of sugar taking place. Boothby and Sandiford confirmed upon dogs the calorigenic action of epinephrin which they obtained on human beings.

Finally, they have calculated that, whereas one milligram of thyroxin induces an extra heat production of 1,008 calories, one milligram of epinephrin increases the basal metabolism only 50 calories. Calculated on the molecular basis, thyroxin is 64 times more potent than epinephrin, and epinephrin is immediate, thyroxin slow in developing its calorigenic powers.

THE PANCREAS

It would lead one very far to discuss the respiration metabolism in diabetes, and no attempt to do so will be made here. I will only mention that in certain unpublished experiments of ... and Chambers, performed with the aid of the respiration ... of the Cornell University Medical College, it has ... tely proved that the basal metabolism of fasting dogs ... with amytal may remain at a constant level for six su... hours, but when one administers insulin subcutaneously ... amytal anesthesia there is often a slow but definite ... the metabolism, persisting for at least five hours. At the ... of this time the heat production may be 20 per cent or more above the normal basal level, the increased metabolism taking place at the expense of an increased combustion of fat, as ... by the respiratory quotient. The very gradual in... the heat production would seem to rule out any second... ... through the adrenal. Control experiments on thy... ...ized dogs have not been carried out. The entire in... ... in the heat production might easily be due to abnormal conditions in the cells brought about by the low level of the blood sugar.

THE PITUITARY

The results of respiration experiments in diseases of the pituitary gland are very conflicting. Plaut (17) reports that,

whereas in diseases of the hypophysis (24 patients) and in hypophyseal obesity (32 patients) the basal metabolism rests within the normal limits, the specific dynamic action of a given diet increases the heat production by only 11 per cent, as against 28 per cent in 39 normal controls. And Liebesny (18) goes so far as to state that in hypophyseal dwarfs there is no specific dynamic action of the foodstuffs whatever.

Plaut affirms that in thyrogenous obesity both basal metabolism and specific dynamic action accord with the normal anticipation.

THE SEX GLANDS

The influence of castration upon the basal metabolism has been reported as being negligible and in other cases as tending to lower slightly the intensity of the oxidative processes. Among the latest workers in this field are Asher and Bertschi (19), who used rabbits in their experiments. They very definitely conclude, ''A direct influence of the sexual glands on metabolism does not exist.'' Castration and ovariotomy had no influence upon the metabolism of rabbits nor had injections of testicular or ovarian extracts.

Murlin and Bailey (20) noted a slight fall in the basal metabolism of two castrated dogs, one of which had been previously thyroidectomized. This contradicts Korentschewsky (21), who states that the fall in metabolism after castration does not take place if the thyroid is first removed, and he attributes the usual post-operative fall in heat production as being due to a diminution in the amount of thyroid secretion ordinarily stimulated by the gonads.

The cause of the development of obesity in the absence of gonad secretion may be exclusively due to a decrease in the amount of muscular movement. Thus, Hoskins (22) has shown that, whereas a normal rat may run in a wheel a distance of 950 miles in one hundred days, a castrated rat may accomplish only half that distance. A hundred days after castration 16 rats ran in revolving wheels only half the distance accomplished by 16 normal controls.

I plead for simplicity of attack upon these problems. I would place the syndrome known as the ''Kinetic Drive'' not inside but outside the organism.

BIBLIOGRAPHY

1. Epstein, A. A., & Rosenthal, N.: Am. J. Physiol. (Balt.), 1925, **71**, 316.
2. Collens, W. S.: J. Biol. Chem. (Balt.), 1925, **64**, 461.
3. Deuel, H. J., Jr., & Weiss, R.: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1924, **21**, 456.
4. Abderhalden, E.: Arch. f. d. ges. Physiol. (Berl.), 1921, **187**, 80.
5. Anrep, G. V., & Daly, I. de B.: Proc. Roy. Soc. (Lond.), 1925, **97**, 450.
6. Aub, J. C.: J. Am. M. Ass. (Chicago), 1922, **79**, 95.
7. Kendall, E. C.: J. Biol. Chem. (Balt.), 1925, **63**, xi.
8. Plummer, H. S.: J. Am. M. Ass. (Chicago), 1923, **80**, 1955.
9. Boothby, W. M., & Sandiford, I.: J. Am. M. Ass. (Chicago), 1923, **81**, 795.
10. Liebesny, P.: Wien. klin. Wchnschr., 1924, **37**, 754; 783.
11. Lauter, S., & Jenke, M.: Deutsches Arch. f. klin. Med. (Leipz.), 1925, **146**, 323.
12. Aub, J. C., Bright, E. M., & Uridil, J.: Am. J. Physiol. (Balt.), 1922, **61**, 300.
13. Muirhead, A. L.: J. Am. M. Ass. (Chicago), 1921, **76**, 652.
14. Aub, J. C., Forman, J., & Bright, E. M.: Am. J. Physiol. (Balt.), 1922, **61**, 326.
15. Aub, J. C., Bright, E. M., & Forman, J.: Am. J. Physiol. (Balt), 1922, **61**, 349.
16. Boothby, W. M., & Sandiford, I.: Am. J. Physiol. (Balt.), 1923, **66**, 93.
17. Plaut, R.: Deutsches Arch. f. klin. Med. (Leipz.), 1923, **142**, 266.
18. Liebesny, P.: Biochem. Ztschr. (Berl.), 1924, **144**, 308.
19. Asher, L., & Bertschi, H.: Biochem. Ztschr. (Berl.), 1920, **106**, 37.
20. Murlin, J. R., & Bailey, H. C.: Surg., Gynec. & Obst. (Chicago), 1917, **25**, 332.
21. Korentschewsky, W. G.: Ztschr. f. exper. Path. u. Therap. (Berl.), 1914, **16**, 68.
22. Hoskins, R. G.: Am. J. Physiol. (Balt.), 1925, **72**, 324.

STUDIES ON VIGOR. III. THE EFFECT OF OVARIAN EXTRACT FEEDING ON THE ACTIVITY OF OVARIECTOMIZED WHITE RATS

E. P. DURRANT

From the Department of Physiology, Ohio State University
COLUMBUS

Since their first use twenty-five years ago ovarian preparations for the relief of various menstrual and accompanying disorders have had much consideration by clinicians. These preparations have been of several kinds: follicular, luteal, interstitial, and of whole ovary; in various vehicles as normal saline, alkali, glycerine, or in dry form. Administration by mouth has usually been preferred and glycerine extracts have come into some degree of favor. For example, Hancher and Rogers (1) have reported recently a number of cases in which the patients showed striking improvement following the use of glycerine extract of whole pig ovary. However, the inherent limitations on clinical observation and deduction, due especially to the variable psychic factors, offer obvious difficulties in reaching dependable conclusions. Clearly, the first problem demanding solution is whether a given extract has any potency whatever. The fact that oöphorectomy in the white rat causes a sharply marked and easily recorded depression in spontaneous activity would seem to offer an unusually favorable opportunity for solving this primary problem. The fact that the data are absolutely objective, being secured automatically without human intervention, is a particularly valuable feature of such investigation in the field of the sex hormones.

In this study observations were made on eight doubly ovariectomized rats and seven litter mate controls from seven different litters. At the ages of thirty to forty-seven days the seven litters were placed in individual activity cages for matching. The cage, described elsewhere (2), consists, in brief, of a cylindrical metal drum with sides of hardware cloth fixed on a rotating axis whose revolutions are recorded by an automatic counter. In free communication with the cylinder is a small sleeping and

feeding compartment (see Fig. 1). The whole is in the main
an adaptation of the apparatus originally used and described by
Stewart (3). The rats remained in the cages from eighty-seven
to two hundred forty-three days before ovariectomy, the average
time being one hundred thirty-three days. At ages varying
.between forty-six and seventy-two days and averaging fifty-eight
the activity took on the cyclic character described by Wang (4)
and Slonaker (5). When curves of the daily activity were

Fig. 1. Cut of recording activity cage.

plotted they showed high peaks (Fig. 2) every four or five days,
corresponding to the estrus cycle as determined by the vaginal
smear method described by Stockard and Papanicolaou (6) for
the guinea pig and by Long and Evans (7) for the white rat.
Using the microscopic findings as a check on the activity curves,
our observations confirm Wang's conclusion that the animal is
"most active during estrus."

After matching as to vigor, pairs of animals of as nearly equal activity and weight as possible were selected from each litter with an additional rat from one of the litters. The more active in each pair was ovariectomized. Through a median dorsal skin incision stab wounds were made over the region of each ovary and the ovary excised after ligation of the uterine horn and its accompanying vessels. The skin incision only was closed by sutures. As the white rat is known to resist infection

Fig. 2. Typical graph of activity of female rat; A-A before ovariectomy; B-B after ovariectomy. The horizontal axis shows the age in days, the vertical gives the number of revolutions per day in thousands.

remarkably well, only ordinary care was taken for asepsis, the skin being simply sponged with mercurochrome solution while the instruments, cotton and sutures used were subjected to a bath of 0.5 per cent lysol. Ether was employed for anesthesia. In a number of experiments in this laboratory sham operations (simple laparotomies) have been shown to have little or no effect on the activity of the animals, so that it was deemed un-

necessary to traumatize the controls. The ovariectomized animals were in most cases returned at once to the activity cages.

As shown by Wang (4) and Slonaker (5), the effect of ovariectomy is to reduce the activity to a much lower level and largely to abolish its periodicity (Fig. 2). Four of the eight castrated rats in this experiment regained their activity to some extent and showed slight evidence of periodicity for a short time, but within twenty days fell to the low level which, with the usual slight daily variations, was maintained through the remainder of the experiment. It will be seen that our experience in this respect is not in entire accord with that of Allen et

Fig. 3. Composite graphs of activity of four normal and eight ovariectomized rats before and during ovarian feeding. X-X period of feeding.

al. (8), who consider animals suitable for testing the effects of follicular extract in five days after the operation.

Hancher and Rogers (1) found glycerine extract of entire ovary most effective both in their clinical work and in experiments on guinea pigs and dogs. It was therefore decided to follow a similar method in this experiment. In preparing the ovarian extract pig ovaries were obtained from a local packing company and within an hour of removal from the animals were cleared of fat and connective tissue as far as possible by mechanical means, the follicles ruptured, the ovaries comminuted, and the whole mass ground in sand. To the mass of tissue and

fluid was then added gradually four-fifths of its volume of glycerine. This was thoroughly mixed and allowed to stand for eighteen hours, after which the liquid portion was expressed through several layers of fine gauze.

When the animals were from two-hundred-seventy to two-hundred-ninety-seven days old and the litter controls still manifesting the typical activity of estruation the feeding was begun, first on a group of four, then after a week on three others, and after a second week on the remaining one, the week interval in this case being allowed for it to attain the usual low and uniform level of activity. Twenty-five hundredths cc. of the glycerine extract was fed daily at 1 p. m. (by means of a specially graduated pipette) just after the day's run had been read. This was continued for twenty-one days, a period equivalent to four or five estrus cycles. Three of the rats were next given three successive doses of 0.5 cc. each at intervals of four hours. Three others were then given three doses of 1.0 cc. each at three and one-half hour intervals. One of this group tolerated with difficulty the entire 1.0 cc. dose, and another refused the third dose entirely, although all took 0.25 to 0.5 cc. with avidity. It should be noted that these doses were relatively enormous, the weight of the rats being approximately one three-hundredths that of adult human subjects. However, no evidence of a toxic effect was detected, except for the refusal of the largest doses by the two rats mentioned.

RESULTS

A careful comparison of the daily activity of the ovary-fed rats with that of their controls and with their respective records before feeding fails to reveal any effect from the extract whatever. The table shows, with other data, the average daily activity of each animal reckoned by ten-day periods. Fig. 3 gives a composite graph of four controls and eight castrated rats plotted from the data given in the table. Three of the controls had to be killed before the end of the experiment on account of otitis media and are omitted from the composite with view to greater exactness. The ten-day periods are indicated on the

Animal	Age in Days	A	B	C	D
C 331 / E 332	111 / 111	4413/11847, 3729/10266, 5322/8220	4744/4826, 3919/4359, 3120/1519, 3153/2091	2062/1205, 2582/867, 4631/206	3722/222, 3670/265, 3322/117
C 353 / E 355	185 / 185	8249/12670, 7070/8922, 4689/6036	5522/2891, 5467/2633, 4652/1843, 3853/1343	3894/1581, 6711/2221, 7262/1656	4235/1656, 8935/1066, 7150/792
C 370 / E 369	177 / 177	7978/11296, 11487/9833, 5100/1078	5781/2743, 4140/1809, 4070/1578, 4408/1491	4865/1522, 4000/2058, 1121/2188	4311/1262, Killed/852, 525
C 381 / D 380	173 / 173	3372/4711, 3970/7819, 3494/5298	4121/1833, 3374/1583, 5194/1959, 4319/1286	4412/1135, 4035/1408, 2074/789	Killed/1440, 1430, 1105
C 390 / E 392	92 / 92	11520/9665, 10869/7948, 8122/9177	8000/4051, 11282/7605, 6972/2419, 7702/1941	5839/1626, 5587/1715, 5279/1582	3211/1392, 6713/1194, 4216/910
C 417 / L 414 / E 416	111 / 276 / 111	8978/5480/7711, 10843/6838/9110, 11565/8254/7013	5935/4491/5313, 6741/2615/7580, 5753/2714/3751, 5404/2306/1784	6660/*/1110, 6018/937, 8201/2645/1171	9609/2741/1901, 9931/2306/1779, 8392/2290/1910
C 126 / E 127	87 / 87	10772/8089, 7667/9076, 4008/7568	4628/1920, 5061/2420, 4567/2733, 5382/1312	4194/1190, 4324/1101, 8832/1112	7489/1033, 6092/1377, 5927/1012

The columns above give the average daily number of turns of the cage run by each animal when averaged for successive ten-day periods.
A—Gives the thirty days before ovariectomy. B—Forty days immediately following ovariectomy. C—Thirty days before the ovarian extract was fed. D—Thirty days in which the extract was fed. Control animals are designated by "C" and ovariectomized by "E". *—Feeding begun one week after ovariectomy.

horizontal axis, the average daily activity in thousands of revolutions on the vertical. The graph exhibits the same facts as the individual records, but with a smoother curve on account of the ten-day averages, instead of daily readings being utilized. As will be seen from the control graph, the feeding was done during a period of increasing activity, hence the failure of augmentation from ovarian feeding is doubly significant. The activity not having been affected, it would be expected from the known correlation between activity and estruation that the vaginal smears would prove negative, and on examination such was found to be the case.

DISCUSSION

It does not seem likely that the hormone, granting its existence, would have been destroyed by glycerine extraction, but rather that it was rendered ineffective by the digestive processes, or for other causes failed to reached the blood stream in potent form or in adequate quantity, since it has been shown by Allen and Doisy (9) that follicular fluid alone, when given subcutaneously, is able to bring about the various vaginal changes of the estrus cycle. Another possibility with preparations of entire ovary, as indicated by the work of Dixon and Marshall (10), is that the luteal incretion to some extent or in some conditions represses follicular activity or perhaps neutralizes the follicular principle sufficiently to prevent the effect characteristic of liquor folliculi collected from isolated follicles.

As bearing on the adequacy of the technic employed to demonstrate the efficacy of ovarian hormones, it may be stated that Wang (4) showed marked restoration of activity following successful ovarian grafts.

SUMMARY

In an experiment with eight doubly ovariectomized and seven litter control white rats, the daily feeding of glycerine extract of whole pig ovary for a period of three weeks had no effect on the voluntary activity of the ovariectomized animals. Thrice daily feeding of large doses was likewise ineffective. In view of the proved adequacy of the method used to detect the

·influence of ovarian hormone these experiments cast further doubt on the efficacy of ovarian preparations administered by mouth.

BIBLIOGRAPHY

1. Hancher & Rogers: This Journal, 1925, 9, 21-34.
2. Durrant: Am. J. Physiol. (Balt.), 1924, 70, 344-350.
3. Stewart: Am. J. Physiol. (Balt.), 1898, 1, 40.
4. Wang: Comp. Pyschol. Monogr. (Balt.), 1923, 2, S. No. 6.
5. Slonaker: Am. J. Physiol. (Balt.), 1924, 68, 294-315.
6. Stockard & Papanicolaou: Am. J. Anat. (Phila.), 1917, 22, 225-284.
7. Long & Evans: The oestrous cycle in the rat and its associated phenomena. University of California Press, Berkeley, 1922, p. 148.
8. Allen. et al: Am. J. Anat. (Phila.), 1924, 34, 142.
9. Allen & Doisy: J. Am. M. Ass. (Chicago), 1923, 81, 819.
10. Dixon & Marshall: J. Physiol. (Lond.), 1924, 59, 276-288.

AN UNUSUAL CASE OF HETEROGENITALISM*

JOHN McDOWELL McKINNEY

From the Endocrine Clinic of the Neurological Institute

NEW YORK

H. W., a schoolboy 16 years of age, born in New York City of Jewish parents, was brought to the Neurological Institute, December 30, 1924, because of backwardness in school and childishness of behavior.

Family History. The mother and father were born in Poland and came to the United States as young adults. They are both living and well. One brother, born of the second pregnancy, died of convulsions at six months. The patient is the youngest child. There were no miscarriages. There is no history of goitre, diabetes, dwarfism, gigantism, migraine, epilepsy, nor insanity in the family.

Developmental History. The labor was at full term, but difficult owing to the presence of fibroid tumors of the uterus. The delivery was instrumental. The child showed no evidence of injury and respiration started normally. There was no evidence of the presence of a dead twin.

The patient was a sickly baby and was subject to frequent attacks of colic and vomiting, which continued through his second year. There was a single convulsion at six months. The patient sat up, cut his teeth, walked and talked at the proper ages. He entered the public school at the age of six.

Patient's History. The patient has had the usual childhood diseases. He had grippe at 12 years. There were no serious illnesses. There is no history of bed wetting, nose bleeding, headache, hay fever, eczema, urticaria nor asthma. The patient broke his left arm at 6 years, which healed satisfactorily. There were no operations.

Present Illness. The first symptom called to the parents' attention was backwardness in school. He has had to repeat every grade and is now in grade 6-B.

It is only within the past two years that the parents have regarded his behavior as abnormal. The patient prefers to play with children much younger than himself, is inattentive, easily distracted and incapable of taking directions. He becomes nervous, confused and loses his temper when he does not comprehend what is wanted of him. He is emotionally unstable, timid, and apprehensive. These symptoms are becoming more pronounced.

No physical abnormality was noted by the parents before bringing the patient to the clinic. When the abnormal breast development was called to their attention the parents seemed quite surprised and stated that this condition did not exist the previous summer. This statement seems to be born out by the patient as he asked for a written permission to excuse him from gymnasium as the other boys had recently taken to teasing him and calling him a girl.

Habits. The patient's appetite is good; he sleeps well; his bowels are regular. He is not over fond of sweets and he has no polydipsia nor polyuria. The parents have never seen any evidence of masturbation nor pollutions.

Endocrine Status. The height is 159.5 cm.; the weight 117¾ lbs.

---

*Heterogenitalism is submitted as a better term than pseudo-hermaphroditism.

(53.5 kgms.) stripped. The head is moderately microcephalic; there is moderate lumbar lordosis; no prognathism; no maxillary torus; feminine contour; broad pelvis. There is hyperextension of all joints and a moderate degree of flat foot. The size of the hands and feet is not disproportionate. The facial type is not characteristic. Growth

has been rapid within the past year, but no measurements were made prior to the present examination. The present measurements are as follows: Torso-leg ratio, 40.5-85 cm.; spread of arms, 159 cm.; Bust (mid-expansion), 79.5 cm.; shoulders (bisacromial diameter), 37.5 cm.; waist, 69.5 cm.; hips at greater trochanters, 89.5 cm.; interpupillary distance, 58 mm.

Skin. The skin is fine, smooth and moist. The nails are bitten off short. There is no eruption. There is a faint pink line on stroking the skin of the chest and abdomen.

Teeth. The teeth are close together, but not crowded. The central invisors are broad, rounded and imperfectly enameled. The lateral incisors are rather small. The canines are well differentiated. The second bicuspids and third molars have not descended.

Hair. The hair of the head is black, thick, coarse and curly. The temporal hair almost reaches the outer edge of the eyebrow on each side. There is no nasal brow. There is beginning axillary and pubic hair and the lanugo on the upper lip and back is darkened.

Muscle. The muscular development is not abnormal. There is no increased muscular irritability nor myoidema. There are no muscle or tendon contractures and no locallized weakness, atrophy or hypertrophy.

Glands. The tonsils are large and the cervical glands are palpable. The axillary and inguinal glands are not enlarged. The tongue papillae are not enlarged. The thyroid is barely palpable.

The breasts are large, of the adolescent female type, and contain readily palpable gland tissue. The nipples are rudimentary.

Pigment. There are no abnormal pigment deposits on the skin, teeth or mucus membrances.

Genito-urinary Organs. The penis is well formed and of about normal size. The prepuce has been circumcised. There is a scrotal fold surrounding the base of the penis. The testes are descended, but are small and soft. Rectal examination revealed a normal prostate. No abnormal organs could be palpated. The patient claims to have occasional erections, although the bulbocavernosus reflex could not be demonstrated. There is no history of pollutions.

Cardiovascular System. The pulse is 84 and the blood pressure 128-60. The blood vessels are rather small.

The general physical and neurological examinations disclosed nothing noteworthy.

Laboratory Examinations. The blood count is as follows: R. B. C., 4,200,000; hemoglobin, 80%; W. B. C., 6,500; polymorphonuclears, 62%; small lymphocytes, 32%; large lymphocytes, 4%; eosinophiles, 2%. The coagulation time (Biffi-Brooks) is 13 min. The blood sugar is 0.09%. The carbon dioxide combining power is 51%. Blood Wassermann examination is negative. Upon analysis the urine is found normal.

X-ray Report. Examination of the skull shows the calvarium to be even in outline but irregular in thickness. The circulatory channels are normally visible. There is no evidence of increased intracranial pressure. The sella is small, but well rounded and wide open. The basal angle is normal. Essentially the examination is not remarkable except for the questionably small sella.

Examination of the thorax shows the trachea to be in the midline. The aortic arch is clearly defined. There are no abnormal shadows in the superior mediastinum.

The intelligence quotient as measured by the Terman test is 0.55 which places the patient in the moron group.

SUMMARY

A boy of 16 years is described showing mental and behavioristic retardation associated with a feminine contour and breast development of the adolescent female type. The penis is well developed and the testes descended, though soft. No abnormality could be discerned in the formation of the generative system with the exception of the soft testes. Rectal examination revealed nothing abnormal.

THE EFFECT OF SINGLE DOSES OF THYROID GLAND ON FOWLS

M. ZAVADOVSKI

Biological Laboratory, Sverdlov University

MOSCOW

In a former article* were published the results of three years of observation on the effects of feeding fowls thyroid gland. The usual symptoms of hyperthyroidism, such as increased excitability, polydipsia, polyphagia, tremors and diarrhea, were recorded. Four peculiar phenomena hitherto unnoticed were described: (1) Premature "experimental" moulting; (2) Replacement of the former colored feathers by depigmented white feathers; (3) From prolonged toxic dosing neuropathological symptoms marked by depression alternating with flashes of excitability, followed by cessation of co-ordinated movements; (4) From further administrations of large doses, death preceded by characteristic tremors.

In all these experiments daily, systematic administration of thyroid or preparations of the gland were employed. This method required much time and trouble, and at the periods of acute poisoning the fowls had to be fed artificially twice a day. Attempts at simplification were therefore made.

Previous investigations had demonstrated that to obtain "qualitative reactions" one administration of thyroid gland was sufficient. These experiments also showed the occurrence of a certain cumulative action of the thyroid; fowls are very resistant to thyroid treatment and can at one administration absorb very large doses, larger than the sum total of daily lesser applications.

The present investigations have been conducted for the following purposes: (1) to arrive at a simpler way of attaining the symptoms of hyperthyroidism, as already described; (2) to get a direct proof of the phenomena of cumulative action of the hormone of the thyroid gland; (3) to discover what single

---

*The effect of feeding fowls on thyroid gland. Zavadowsky, B.: This Journal, 1925, 9, 125.

dose will be fatal for fowls, and to study the accompanying neuropathological phenomena.

Among other possible simpler methods grafting of the gland was tried. For this purpose a mongrel black hen, utilized in previous studies as a control bird, was used. This hen had in the interim been experimented on with inorganic iodine. These experiments will be published in a subsequent article. This fowl on July 31, 1923, had its feathers plucked away under the wing, and there were grafted under the skin five dogs' thyroid glands.

Aug. 5. The skin on the spot engrafted became inflamed.

Aug. 7. The hen was in a typical depressed or excited condition and would not allow handling; the feathers were firm.

Aug. 17. The feathers were still firm, but tufts of white feathers appeared at the site of the graft.

Aug. 20. The feathers on the spot operated on were grown to full length, and had large white tips. There was no moulting.

This hen in the previous control experiments had had the feathers under the wing or the legs repeatedly plucked, and on each occasion there had grown pure black feathers; therefore the partial depigmentation in this case must be attributable solely to the action of the glands implanted. In this case all the previous observations were repeated, namely, that *pigmentary phenomena require very much less thyroid than those of moulting;* thus, in this experiment, despite the summer season when normal moulting might have been expected, the grafting caused whitening of only the new growth of feathers.

Further experiments were carried out using single doses of desiccated thyroid gland. For this purpose material from horses was prepared in advance during the winter. The glands were cut into fine shreds and desiccated in thermostats at a temperature of 40-50° C. These experiments showed convincingly the correctness of the former hypotheses. The phenomena of discoloration above mentioned were reproduced, and were even more pronounced than before. However, the resistance of the birds to additional administration of thyroid gland was exhibited to an unexpected extent.

Experiment 1. A spotted hen; weight 1725 gm.

July 18, 1923. Fifteen grams of desiccated thyroid gland was given.

July 25. The feathers were dropping profusely.

July 27. The weight was 1400 gm. The hen was very naked and highly excitable.

July 31. It was literally stripped of all its plumage except for

a few feathers on the tail and the down. All the rest of the body was covered with little stumps of growing feathers.

Aug. 7. The stumps of the young feathers were beginning to stand out; but the newly developing crest, instead of the previous straw color, was pure white, with weakened outlines compared with the former black.

Experiment 2. A yellow hen; weight 1660 gm.

July 24, 1923. Twenty-five grams was administered.

July 27. The weight was 1650 gm. Moulting was marked.

July 31. Many feathers were lost.

Aug. 2. It had almost caught up with the spotted hen.

Aug. 5. It was more naked than the spotted hen.

Aug. 7. The weight was 1415 gm. The hen was almost completely naked and the remaining feathers were very weak. On each wing was one straw-colored feather. On the left wing there were also three covering feathers; on the occiput were 11 feathers; on the back, 2; near the tail, 5; on the belly, 10. The remainder of the body was covered with stumps of newly-grown feathers. (See Fig. 1.)

Fig 1   A yellow hen in the state of moulting (Experiment 1).

Aug 14. The feathers were growing rapidly, and had white spots on them.

Still larger doses were next administered and the phenomena of depigmentation under similar conditions on pure black fowls were verified

Experiment 3. A black hen; weight 1632 gm.

July 31. Fifty grams fowls siccated thyroid gland was administered.

Aug. 1. The hen was   ut somewhat sickly and depressed.

Aug. 2. It was depre   alive and ate well.

Aug. 5. The feathers   se. The bird was in a very nervous condition.

Aug. 7. The conditio   ssed excitement continued.

Fig 2   A pure black hen in the state of moulting (Experiment 3)

Fig 3   Same hen as in Fig 2 with renewed feathers

Aug. 8. The plumage scarcely held; fresh stumps were already discernible.

Aug. 14. The hen was almost entirely naked, and in an excited condition.

Aug. 16. It was very naked, but less so than the yellow hen. Extensive growth of white feathers was noted.	(See Fig. 2.)

Aug. 21. There was very marked moulting.

Sept. 20. The new plumage was complete and there were almost as many white as black feathers. The weight was 1547 gm. (See Fig. 3.)

*Experiment 4.	Minorca No. 15; pure black; pure bred;
weight 2350 gm.*

Aug. 7.	Twenty-five grams was administered.

Aug. 10.	The feathers were already moulting.

Aug. 14.	There was marked moulting; the bird showed both depression and excitement of marked degree.

Aug. 16.	It was naked, but less so than No. 3.

Aug. 28.	The hen was still not quite naked; growth of many white feathers was observed.

Sept. 1.	There was a plentiful covering of white feathers.

Additional administration of from 15 to 50 gm. of desiccated thyroid gland was thus proved convincingly to be sufficient to produce fundamental symptoms of the phenomena of moulting and the consequent depigmentation. As soon as the new feathers begin to appear, about two or three weeks after the administration of the gland, the hormone effect appears and lasts for not less than three weeks. It is remarkable also that the same regular periods of the first moulting and the first growth of white feathers were observed in this experiment as in the one previously reported. As stated in the first article, moulting starts in from seven to thirteen days, and the white feathers appear in from twenty-five to twenty-nine days, depending upon the dosage. The spotted hen began to moult on the seventh day; the yellow hen between the third and sixth; the black in Experiment 3 on the sixth; and the Minorca on the seventh. Weakening of the roots of the feathers rather than the natural course of moulting accounts for the reaction on the third day in the case of the yellow hen. White feathers appeared on the spotted hen on the twenty-second day; the yellow hen on the twenty-first; the black hen of Experiment 3 on the twenty-seventh; and the Minorca on the twenty-first day.

Thus in both cases there was a tendency towards acceleration of the phenomena; this agrees with previous observations that stronger doses of the hormone hasten the reaction. This problem of the effect of increased doses on the degree of the reaction was tested in accordance with the new method. To this end, and also to discover the minimum dose which would produce a noticeable result, the following experiment was devised:

Experiment 5. Black hen.

Aug. 17. Five grams of desiccated gland was administered.

Aug. 23. Some feathers began dropping; in general moulting was not marked, but feathers could be pulled out more easily than usual.

Aug. 28. Moulting was noticeable, but only in small amounts. The plumage was thinner and ragged. The weight was 1729 gm. Twenty-five more grams was administered.

Sept. 4. The hen became markedly naked.

Sept. 20. There were many white feathers.

This experiment confirms the fact that a certain relation exists between the amount of thyroid substance administered and denudation and depigmentation. This was manifested not only by the slight moulting of the black hen (Experiment 5), but also by the long duration of the period of ineffectiveness in some earlier experiments with smaller frequent doses, when the first moulting was on the eleventh day and the growth of white feathers on the twenty-seventh, instead of the shorter periods when the maximum doses were given. A dose of 5 gm, may be considered as approximately the minimum additional dose sufficient to produce a noticeable reaction in the plumage and in the organism of the bird.

Experiment 6

In order to determine this question finally two chickens, three to four months old, weighing respectively 1035 and 1040 gm. each, were given 2 gm. of desiccated gland.

Aug. 28. Six chickens weighing from 389 to 575 gm, were given 5 gm. each.

Sept. 7 and 11. The two first under observation showed very slight moulting and only a few of the six others showed signs of moulting.

Sept. 17. It seems sufficiently evident that the minimum dose of thyroid gland sufficient to cause slight but noticeable symptoms of moulting in fowls weighing 1 kg. may be estimated at 1-2 gm. These figures apply to the autumn season and vary in accordance

with individual peculiarities and the species of fowl. Further research is needed.

The fowls were found to be astonishingly resistant to large doses of thyroid. Possibly there are no limits to this resistance. Doses of 25 and 50 gm. of desiccated gland seem to be the most practicable for the experimenter who has to thrust into the bird's beak lumps of the gland. Even with the maximum doses the fowls betrayed no signs of that nervous pathological depression, a condition approaching lethal poisoning, such as was described in the previous article. Therefore, particular interest was felt in verifying the cumulative effect of the poison.

Experiment 7. A small black hen; weight 1400 gm.

July 31-Aug. 4. Four grams of desiccated gland was administered daily.

Aug. 4. There was noticeable weakening of the feathers; they fell out at a touch of the hand.

Aug. 6. The hen was found dead, in the attitude typical of thyroid poisoning, the feathers scarcely holding to the body.

In six days this hen was fed 24 gm. of the gland, while doses of 25 gm. were taken by fowls of the same weight without any sign of marked poisoning, thus demonstrating the cumulative effect of the gland. Further research is needed, however, as to the characteristics and operation of these phenomena. It is probable that with limited administrations the bird's organism manages to discharge a considerable part of the substance before it is absorbed into the blood; while with smaller but systematic doses the whole of the hormone introduced is assimilated. It is almost impossible under the conditions of our autumn experiments to administer a lethal dose to fowls. The method of additional doses facilitates the observation of all the phenomena hitherto described and renders them extraordinarily effective. It enables the experimenter to strip the fowl in a fortnight and also to get in the third week an abundant growth of white feathers without the accompanying symptoms of acute poisoning or risk of fatal termination. A further advantage in this method is that there is a constant change of plumage, a complete renewal. This led to the discovery of the fact that *the new plumage which makes its appearance after the experimental moulting is apparently much softer than the old ordinary plumage.* This has not been verified, however, by morphologic and microscopic analysis of the nature of this newly grown plumage.

The new method has made it possible to study one other

heretofore unanalyzed phenomenon. In the first article the fact that it was easier to get an effective moulting in autumn than in spring was mentioned. The extent to which this phenomenon is connected with the influence of the sexual hormone, the action of which is opposite to that of the thyroid, was studied. It has now been convincingly demonstrated that the *growth of the feathers* plays the leading part; *the young feathers that have grown just after the experimental moulting are very much less liable to be moulted a second time.*

Experiment 8. A spotted hen, which had moulted again after a dose of 15 gm. on July 18

Aug. 14. Twenty-three grams of thyroid gland was administered.

Aug. 21. A test proved the firmness of the feathers. The weight was 1325 gm.

Aug. 23. Thirty grams was administered.

Aug. 28. The plumage was still quite firm. Twenty-five grams was administered.

Sept. 4. The feathers were slightly weaker on the nape, but, generally speaking, there was nothing resembling moulting. The fowl seemed depressed.

Sept. 9. There was slight moulting of feathers on the nape. The depression continued up to the time of writing, Sept. 15.

Experiment 9. A yellow hen which had moulted after administration of 25 gm. on July 24

Aug. 23. Thirty grams of desiccated gland was administered.

Aug. 28. The feathers were perfectly firm. The plumage was decidedly softer and smoother than on the other fowls.

Sept. 4, 7, 14. The feathers were firm.

Experiment 10

The experiment was conducted on a hen to which doses of 1 gm. had been regularly administered from Aug. 2 to Aug. 16, resulting in the production of partial moulting accompanied by a change from black to white plumage.

Aug. 17. Twenty-five grams of gland was administered.

Aug. 23. The bird strayed about, but the white feathers that had appeared after the preceding doses were retained.

This shows that the degree and nature of moulting in fowls depend largely on the age of the feathers. That such feathers are not absolutely immune, however, to an experimental second moulting was ascertained on the spotted hen after a third application of a strong dose of thyroid. In this, as in its influence on the other functions of the organism, the thyroid hormone appears to be a typical catalyser.

SUMMARY

1. One strong dose of thyroid gland is sufficient to induce specific phenomena of moulting and depigmentation on fowls as described in a previous article.

2. Fowls exhibit extraordinary ability to withstand large single doses; even 50 gm. of thyroid gland at a single dose fails to educe those symptoms of acute poisoning previously noticed, such as neuropathologic fits, ending in death with tremors and convulsions.

3. The fact of cumulative action of the hormone of thyroid gland is confirmed. Fowls can endure at one application much stronger doses than in constant daily smaller administrations.

4. The periods previously given for the beginning of moulting and the appearance of white feathers have been corroborated with the reservation, however, that the rapidity and extent of the reaction depend on the size of the dose, maximum doses inducing moulting on the sixth day and the first appearance of white feathers on the seventeenth to the twenty-first day. When smaller doses are administered the periods are respectivly eleven to thirteen days and twenty-nine days.

5. The minimum dose of thyroid gland which will induce a noticeable reaction in moulting and depigmentation on fowls was found to be 1-2 gm. desiccated gland per kilo from June to October.

6. The new growth of feathers after experimental moulting can be subjected to a second moulting in the same way only with great difficulty. The growth of the plumage, therefore, is the essential factor in determining the degree of the reaction to the thyroid gland substance.

7. The new method of single doses enables the experimenter within a fortnight to deplume any fowl and in four weeks to be sure of an appearance of white feathers.

8. The new plumage that grows after experimental moulting is markedly softer than the normal.

9. The fact that the growth of the new feathers comes about in three weeks after thyroid feeding proves that the action of each administration continues not less than three weeks after

the introduction of the hormone into the organism. This fact corresponds with the characteristics of thyroxin stated by Kendall*, in men and mammals. The action of thyroxin on fowls will probably be investigated at a later date.

10. Grafting dog thyroid glands in fowls produced whitening of the feathers at the site of the operation, but no moulting. This proves that the thyroid gland acts more sensitively to produce depigmentation than moulting—a fact already noted at the outset of the former experiments.

*The physiologic action of thyroxin. This Journal, 1919, 3, 156-163.

Editorial

PARATHYRIN (COLLIP)

Organotherapy since several years has been bombarded with ridicule and censure. In the enthusiasm for applying this novel therapy endocrine extracts have been prescribed in innumerable conditions where the theoretical clinical indications for their usage have been of whimsical, flimsy texture. Rebuke for such hazy therapeutics has been warranted. More lamentable, however, was the failure to achieve improvement in endocrine deficiencies where the fundamental indications for glandular therapy were positive and sound. It is but a short time since pancreatic therapy for diabetes mellitus was utterly futile. How different now with insulin. It is no simple matter to produce potent extracts. Hormones are delicate structures, easy to destroy in the process of manufacture and harmed sometimes by intestinal juices.

It is therefore a matter of congratulation that Professor Collip of the University of Alberta, Canada (who it will be remembered contributed to the isolation of insulin), has added another potent extract to the field of organotherapy. Whether or no his extract contains a perfect parathyroid hormone or all the active principles, if there be more than one, is impossible to state at this time, but most emphatically *it does contain a something that does something.* In other words, injection of this extract exercises a profound influence on the blood calcium content, just as insulin affects the blood sugar, only in an opposite direction. It raises the blood calcium, whereas insulin lowers the blood sugar. A further proof of its potency is evidenced by the alarming possibilities from overdosage. Collip has produced hypercalcemia experimentally in dogs, with fatal result and such complete clotting of the blood that at times no serum could be obtained for blood calcium determinations.

It is earnestly to be hoped that clinical experimentation with this potent parathyroid extract will shed some light on the mys-

teries of parathyroid function. Despite the prodigious amount of investigation that has concerned itself with these tiny glandules, much remains to be explained, confirmed or disproved. We know that tetany results from clinical or experimental removal of these glands. We know that the blood calcium sinks to a low level under these circumstances. We know that Collip's parathyrin will raise the blood calcium promptly and thus relieve the tetany; not only has this been confirmed in animals experimentally, but already in a few cases of human tetany following thyroidectomy.

Is tetany the only clinical syndrome that follows parathyroid deficiency? On the face of it, this would seem unlikely. It is to be remembered that juvenile cataract has complicated juvenile tetany and been reproduced in animals following parathyroidectomy. Curious punctate enamel defects in the teeth have also been noted clinically and produced experimentally. Further clinical experimentation will probably follow two directions, a trial of parathyrin in diseases supposedly involved with a disordered calcium metabolism (such as rickets, osteomalacia, possibly certain types of delayed coagulation, chronic ulcers, urticaria, etc.) and a trial in diseases where acute or chronic spasm plays a prominent role (epilepsy, asthma, hay fever, vasomotor rhinitis, angioneurotic edema, spasmophilia, hypertension, etc.).

At first thought, it would seem fantastic to assemble such a weird company under one roof, and it is unlikely that many of them will be benefited by parathyroid therapy. However, we must admit that we know very little concerning the etiology of any of them, and a therapeutic trial of a potent extract has some justification. At least it may result in squelching the rumors of parathyroid participation. And again it may be found that parathyrin possesses pharmacodynamic powers like adrenalin and pituitrin, of benefit in conditions quite unrelated to parathyroid function.

However it may turn out, the door of opportunity is open. Much or little may come of it. Let us hope that the clinical fishing expedition that will inevitably result will be conducted soberly and judiciously with accuracy and discrimination. And

meanwhile it will be prudent to beware of premature announcements.

It is gratifying that the same firm that pioneered so well with insulin has undertaken the manufacture of this new parathyroid extract.   H. L.

Abstract Department

The increase of adrenin action by amino acids (Weiterer Beitrag zur Kenntnis der Wirkungssteigerung von Adrenalin durch Aminosäuren). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1924, **206**, 154-161.

Aliphatic, homo- and hetero-cyclic amino acids (glycine, alanine, glutamic acid, d- and l-tyrosine, di-iodotyrosine, tryptophane, and histidine) in concentrations of 1:25,000 or less, increase the action of adrenin on the surviving large intestine of the guinea-pig. Pyrrolidonecarboxylic acid, the anhydride of glutamic acid, is without action.—A. T. C.

Oxygen consumption in the adrenals (Ueber den Sauerstoffverbrauch in den Nebennieren). Broening (A.), Arch. f. d. ges. Physiol. (Berl.), 1924, **205**, 571-577.

Electrical stimulation of the splanchnic nerve increases oxygen consumption in the adrenals. Since during this stimulation the adrenin content diminishes, the oxygen consumption can be taken as measure of the intensity of the work of the adrenals. Injection of small doses of thyroid extract produces increase of oxygen consumption. Larger doses decrease it. It is decreased by large or small injctions of pancreas extract. Thyroid extirpation has no definite effect on this oxygen consumption (perhaps a slight decrease). Since adrenin secretion is not affected by thyroid or pancreas injection, the authors conclude that the thyroid and pancreas affect the cortex particularly.—A. T. C.

An endocrine factor in the chemical control of body temperature. Cannon (W. B.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 162-165.

A number of observers have shown that secretion from the adrenal medulla is capable of influencing the rate of metabolism in the body, thus accelerating oxidative processes. Employing the denervated heart in animals surviving and living normally, it was found that the organ is influenced only by temperature changes and by agents brought to it in the blood stream, especially adrenin, to which it is extremely sensitive. Animals thus prepared showed accelerations of heart-rate varying from 12 to 43% when taken to a cold room, from 34 to 43% when placed in an ice box, of 43% when held in the lap and exposed to the cold draught of an open window,

and between 27 and 64% when cold water was introduced into the stomach. If the adrenal glands were rendered inactive the effects did not occur. In cats with intact adrenals an injection of a suspension of dead typhoid bacilli produced fever having a characteristic course, with erection of the hairs and shivering during the maximum height of temperature. If the adrenal glands were rendered inactive by the removal of one and denervation of the other, injection of dead typhoid bacilli caused only a slow rise which in some instances was very slight. The author suggests that the response of the adrenal medulla during toxic fever is serviceable to the organism.—I. B.

A case of virilism associated with a suprarenal tumour. Holmes (G.), Quart. J. Med. (Oxford), 1925, **70**, 143-152.

A case is recorded of a young woman in whom a large, slowly growing tumor of the right suprarenal body was associated with changes in the sexual organs, disturbances of the sexual functions, alteration in the secondary sexual characters, and psychical changes, all of which symptoms disappeared within a relatively short time after the removal of the tumor and left the patient again an apparently normal woman. This subject had been under observation for 11 years, two previously to operation and nine since. Many similar cases from the literature are cited by the author, and additional clinical evidence is put forward to show that disease of the suprarenal cortex, and especially such forms as increase its functional elements, can influence the development or state of the sexual system. The author considers that the cases recorded, and especially those in which, after the removal of the tumor, the symptoms disappeared, afford evidence that must now be regarded as conclusive that an internal secretion derived from the cortex of the suprarenal bodies, when in excess, tends in women to diminish the female and increase the male primary and secondary sexual characters. He also suggests that there is abundant evidence to show not merely that active growth and development, in abnormal as well as in normal circumstances, of certain organs of the body, and especially the sexual organs and related systems, are dependent on internal secretions, but also that the growth when attained requires the continuous influence of these secretions and in their absence may regress.

—Med. Sc., **12**, 28.

Two cases of mytilism with anaphylactic shock treated with adrenalin injection. Henrichsen (S. L.), Ugesk. f. Læger (Copenhagen), 1923, **85**, 743-745.

In two cases of mussel poisoning with severe anaphylactic phenomena the author procured strikingly good effects from adrenalin injections.—K. H. K.

Effect of epinephrin by oral administration. Menninger (W. C.), J. Am. M. Ass. (Chicago), 1925, **84**, 1101-1102.

This study is based on a series of observations on the administration of epinephrin by mouth in various types of hyperthyroid cases. To date, a series of fourteen observations has been made on nine patients. Of this group, three have given a very definite and in one case a marked reaction, and two others have given slight reactions. Of the three cases in which the reaction was marked, the blood pressure rose (systolic) 30 mm. in one case, 50 mm. in the second and 110 mm. in the third. The pulse remained practically constant in the first two, but increased 52 beats a minute in the third. In all three cases, epigastric and substernal pain and nausea occurred. Vomiting, sweating and increased tremor occurred in two cases. In the two cases giving slight reactions, the blood pressure (systolic) rose in one case 12 mm. with a pulse increase of 20, and 18 mm. in the second with a pulse increase of 10. In both cases there was epigastric "burning" and distress. These reactions were slight and might be disregarded, excepting that control observations with smaller doses on the same patients produced no objective or subjective effects. At present, conservatively, the only conclusion to be made is that epinephrin may produce marked systemic effect on the circulation in some cases of hyperthyroidism when administered by mouth, the effect resulting from absorption through the gastro-intestinal canal and not from the mouth or throat.—A. M. A.

Studies in Addison's disease. Rowntree (L. G.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 426-450.

A summary of the results of treatment of 47 cases of Addison's disease in the Mayo Clinic since 1912, representing approximately one in every 6600 patients seen. The prognosis in these patients is extremely grave. Irrespective of the amount and intensity of the treatment, approximately two-thirds of the cases are fatal within a year. Treatment consists essentially of forced substitution organotherapy. At best, therapy can only combat functional insufficiency of the suprarenals. The Muirhead treatment should be given a fair trial in every case of Addison's disease with due respect for individual tolerance. Supplementary measures to combat the associated symptoms and underlying pathological process should likewise be instituted.—I. B.

Studies in adrenal insufficiency. Stewart (G. N.) & Rogoff (J. M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 394-397.

The adrenals were removed in 36 dogs at 2 operations. All the animals died after varying intervals. Seven received intravenous injections of Ringer's solution with dextrose. Two of these lived more than 30 days after the removal of the second adrenal,

The author describes a syndrome of infantilism and diabetes insipidus in a boy 14 years old who had signs of involvement of both the anterior and posterior lobes of the pituitary gland, which, however, as indicated by roentgen examination of the sella turcica was not definitely increased in size. A thorough presentation of the case is given from the morphologic standpoint (Viola's anthropometric method) and from the biochemical standpoint, with particular consideration of the hydric exchange. In relation to the anterior lobe the patient showed: deficient stature, short and thin bones, lower extremities relatively long, arrest of development of the genital organs and absence of the secondary sexual characteristics, rough skin, and well developed intelligence. In relation to the postpituitary, the most essential sign was hydruria (from 14 to 19 liters of urine in 24 hours), in which the hydric excretion through the urine and the feces was superior to the amount of water introduced through the aliments. This was accompanied by polydipsia, which, if not satisfied, gave rise to serious phenomena of abstinence, intense intestinal stasis, marked increase in the elimination of chlorids, with alteration of carbohydrate metabolism. The polyuria was only temporarily reduced by the administration of pituitary extracts, especially by hypodermic injections of postpituitary preparations. After an elaborate critical review of the pathogenic theories of diabetes insipidus the author concludes that while in his case there was evidence of a lesion of the neurohypophysis, in many other cases diabetes insipidus depends on a lesion of the centers for diuresis located in the optopeduncular region and in the floor of the third ventricle. These centers function under the stimulus of the hypophyseal secretion which reaches the same by way of the infundibulum and the tuber cinereum. The diagnosis of the seat of the lesion in diabetes insipidus must be made in each clinical case from the consideration of the particular individual symptoms and of the concomitant syndromes, because polyuria may occur if the hormonic stimulus is lacking, if it cannot reach the centers of the diuresis because of defective canalization, or if the centers do not react to stimulation because of lesions within them.—Arch. Neurol. & Psychiat., **13**, 516.

Antagonistic action of posterior pituitary extract and insulin. Moehlig (R. C.) & Ainslee (Harriet B.), J. Am. M. Ass. (Chicago), 1925, **84**, 1398-1400.

From work performed on diabetic patients, Moehlig and Ainslee believe that pituitary extract injections improve the muscular asthenia to a great extent. This is true despite the fact that the patients, for the purpose of the work, are not placed on a diet. Patients with hypopituitarism suffer from asthenia, and fatigue is easily induced. The opposite is true in cases of hyperpituitarism. Posterior pituitary extract injected into normal rabbits produces, as

a rule, a slight rise in blood sugar. Posterior pituitary extract, when injected simultaneously with insulin, prevents the fall produced by the latter. Posterior pituitary extract, injected during insulin hypoglycemic convulsions, produces a rapid rise in blood sugar, with subsequent recovery of the rabbits. The point of attack, of the pituitary extract seems to be in the periphery; viz., the skeletal muscle metabolism.—A. M. A.

Juvenile diabetes insipidus (Note cliniche, anatomiche e di patogenesi sul diabete insipido giovanile). Pincherle (M.) & Magni (L.), Arch. di patol. e clin. med. (Bologna), 1924, 3, 261-289.

This is a study of 5 cases of diabetes insipidus in young persons. Two of the patients died from acute intercurrent disease, and came to necropsy. The authors, after a short but complete exposition of the different theories (endocrine, nervous, mixed) of diabetes insipidus and of the 5 clinical histories, give the anatomopathologic findings in the 2 cases, which seem to confirm the duality of the causes of the disease advanced in some of the pathogenic theories. In one case they found serious and extensive lesions of the hypophysis, with signs of active inflammatory reactions and advanced sclerosis, together with moderate neuroglial proliferation and slight degenerative lesions of the tuber cinereum. In the other case in which diabetes insipidus had been caused by what turned out to be a mild form of epidemic encephalitis, extensive and very severe degenerative lesions of the ganglionic cells of the tuber cinereum were found accompanied by intense phenomena of neuronophagia and perivascular infiltration, while the pituitary gland did not show any histologic alteration. These two diverse findings have led the authors to conclude in favor the dual neurohypophyseal conception in the pathogenic interpretation of the disturbed hydric exchange which is the basis of diabetes insipidus. In the majority of such cases the hypophysis or the tuberal centers or the important connections existing between the gland and the latter are altered, either separately or at the same time.—Arch. Neurol. & Psychiat., 13, 520.

Pathology of the hypophysis. III. Chronic hypophysitis; fibrosis. Simonds (J. P.) & Brandes (B. S.), J. Am. M. Ass. (Chicago), 1925, 84, 1408-1410.

It is evident from the 7 cases reported by Simonds and Brandes that, with advancing age, in many persons the hypophysis undergoes fibrosis, and the body does not receive the normal amount of the secretion of this gland. Fibrosis of the anterior lobe of the hypophysis occurs with moderate frequency in persons past 50. This condition is apparently due to arteriosclerosis of the vessels of the hypophysis. The character of the lesion is such that it must interfere with the function of the glandular portion of this organ. This,

suggests one of the reasons for the failure of efforts at rejuvenation that are directed to the restoration of only one gland of internal secretion. One case of the series here reported appears to be true chronic hypophysitis. In spite of the negative Wassermann test, other findings in the body suggest the possibility of syphilis as its cause.—A. M. A.

Dystrophia adiposogenitalis, with atypical retinitis pigmentosa and mental deficiency. The Laurence-Biedl syndrome. Solis-Cohen (S.) & Weiss (E.), Am. J. M. Sc. (Phila.), 1925, **169**, 489-505.

Four of 8 brothers and sisters of Italian parentage exhibited marked adiposity with mental deficiency, genital dystrophy and diminution of vision. Two of the abnormal children showed polydactylism. The eye-grounds showed atypical retinitis pigmentosa. The fat distribution was largely of the girdle, mons and mammary type. A hypophyseal lesion could not be proved. Roentgen ray examinations of the sella region did not show conclusive changes. No anomaly of osseous development was found. Sugar tolerance tests did not indicate pituitary disease. Basal metabolism was below normal in 3 of the children. Both parents and children gave negative Wassermann reactions. The thyroid glands were palpable and within ordinary limits of size and consistency. There was no lymphadenopathy, and no history of rickets. The family history disclosed no marked adiposity, visual defect, polydactylism, deafness or idiocy. The 4 unaffected children seemed entirely normal; one, indeed, was uncommonly bright and active. Hormone therapy (pituitary-thyroid) seemed to correct amenorrhea in the older girl, but otherwise was without effect on any of the children. Subjective improvement in the sight of the elder girl may have been the result of hormone therapy, but may with equal probability be referred to suggestion, or to the general improvement of nutrition attending hospital care.—R. G. H.

Three cases of pernicious anemia and diabetes mellitus with a note on the apparent ineffectiveness of insulin in the presence of a profound anemia. Adams (S. F.), Med. Clin. N. Am. (Phila.), 1925, **8**, 1163-1170.

During the past 5 years there have been approximately 1000 patients with pernicious anemia at the Mayo Clinic, and approximately 2000 with diabetes mellitus; in only the 3 cases here reported were the two diseases combined. The author was able to find but one other instance of this combination in the literature, that of Parkinson, who, in 1910, observed a case of pernicious anemia terminating in acute diabetes. Insulin was apparently unable to reduce the blood sugar in 2 of the patients reported.—I. B.

Insulin. Banting (F. G.), Internat. Clin. (Phila.), 1924, 4, S. 34, 109-116.

A brief outline of the principles underlying the action and use of insulin. The pathologic physiology occurring in diabetes mellitus is discussed. The necessity for co-operation between physician and patient is particularly stressed, including the need for a knowledge by the patient of the methods of urinalysis, preparation of a diabetic diet, and the knowledge as it pertains to symptoms and treatment of overdosage of insulin. In instances of diabetes with tuberculosis, insulin enables the use of proper nourishment with which to combat the tubercular infection. Patients generally regarded as bad surgical risks may be properly protected from the accidents of anesthesia by the use of insulin. Regardless of the severity of the disease it has been found that by carefully adjusted diet and dosage of insulin, all patients may be maintained sugar-free. This is a very fortunate circumstance, as there is ground for the belief that when the strain upon the pancreas is relieved there is regeneration of the islet cells of the organ. In some instances the sugar tolerance is increased to such a point that insulin is no longer required. Diabetes mellitus is fundamentally a disordered metabolism, primarily of carbohydrates, and secondarily of protein and fat. Insulin is not a cure for diabetes; it is a treatment. It enables the diabetic to burn sufficient carbohydrates so that proteins and fats may be added to the diet in sufficient quantities to provide energy for the economic burdens of life.—I. B.

Anhydremia with insulin and water intake. Drabkin (D. L.) & Shilkret (H.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, 22, 369-371.

Doses of insulin were given to dogs, some of which had been water starved for several days and others of which had received 800 cc. of water per day. The authors note that dogs, desiccated through water-starvation, when given large doses of insulin developed a more severe anhydremia than the dogs which had water. Convulsions were not observed in the desiccated animals, although they invariably appeared in the others. Glucose did not prevent the death of the water-starved dogs. The non-desiccated animals immediately recovered after glucose administration.—J. C. D.

Diabetes mellitus, a contribution to its epidemiology based chiefly upon mortality statistics. Emerson (H.) & Larimore (L. D.), Trans. Ass. Am. Physicians (Phila.), 1924, 39, 290-303.

The prevalence of diabetes mellitus in New York City is discussed. In 1866 there was recorded one death from diabetes for each 2437 deaths from other causes, but in 1923 there was one death from diabetes for each 51 deaths from other causes. The

increase in incidence and death rate from diabetes in this country, and in New York in particular, has been more rapid than that of any other disease for which we have records in the past 50 years. This increase is most marked among women of all ages, and among men and women over 35 years of age in particular. Persons of Semitic stock show the highest death rates, while the negroes show the lowest. It is not thought that the racial element is of fundamental importance since many elements of occupation, economic status, dietetic habits, etc., may be sufficient to explain the statistics in what may be fairly considered a disease of fatigued function in the great majority of cases. Seasonal variations in death rates, calculated upon a monthly basis, are apparently significant. This may or may not be due to seasonal incidence of intercurrent infections. Geographical distribution of the disease as measured by death rates in the United States appears to be explicable on the basis of differences in the age-grouping, race, economic status and occupation of the people, high rates being found where there is a high proportion of the population in the later decades of life, after 45 years, where there are many Jews, and where per capita wealth is high. Where life expectancy is high there is often a lower diabetic death rate than in states where life expectancy is low. It is believed that changes in food habits in the United States have contributed to the increase of diabetes, and that the higher carbohydrate element and greater food intake are the cause of overfatigue of the function of sugar tolerance.—I. B.

Observations on severe juvenile diabetes. Geyelin (H. R.) & Ladd (W. S.), Tr. Ass. Am. Physicians (Phila.), 1924, 39, 308-316.

This is a report of the progress of 9 instances of juvenile diabetic patients who have been under continuous treatment with insulin for 18 months or longer. No definite conclusions are drawn concerning the question of sugar tolerance under prolonged and continuous insulin treatment, though physical and mental well-being, once established, continues to exist, and the children are developing at approximately the same rate as the average normal child. The authors believe that every effort should be made to keep the patients as nearly sugar free as possible, and that continuous sugar freedom is the goal to be aimed at in the treatment of every case of diabetes.—I. B.

Heredity of diabetes. Hansen (S.), Ugesk. f. Læger (Copenhagen), 1924, 86, 341-344.

. . The author considers diabetes as a hereditary disease. He believes that most cases are isolated because its origin depends upon a coincidence of disturbances rather than upon a single factor. This is illustrated by a series of genealogical tables.—K H. K.

Treatment of diabetes by raw fresh gland (pancreas). Hollins (T. J.), Brit. M. J. (Lond.), 1925, i, 503-504.

Hollins reports the successful use of fresh raw pancreas by mouth in the treatment of "about six" diabetics. A striking case is cited of an engineer with a severe attack, with ketonuria, who failed to improve under Allen treatment, who became sugar free and gained weight under raw gland treatment. His blood sugar fell to 0.13%. Marked glycosuria immediately recurred upon intermission of the treatment. The author insists that absolute freshness of the gland is essential to its efficacy. He believes that a tablespoon full (which is adequate dosage) every day or two is less distasteful to the patients than are frequent insulin injections.
—R. G. H.

Hypoglycemia. Jonas (L.), Med. Clin. N. Am. (Phila.), 1925, 8, 949-956.

Hypoglycemia has become an important clinical entity since the discovery of insulin. Mild hypoglycemia may also be observed in myxedema, cretinism, hypopituitarism, Addison's disease, progressive muscular dystrophy, and following subtotal thyroidectomy for exophthalmic goiter. Weakness, sweating, rapid pulse, and nervous phenomena are the most outstanding clinical features of hypoglycemia. Treatment consists in the administration of carbohydrates.—I. B.

Pancreatic and hepatic activity in diabetes mellitus. Jones (C. M.), Castle (W. B.), Mulholland (H. B.) & Bailey (F.), Arch. Int. Med. (Chicago), 1925, 35, 315-336.

An unselected group of 68 diabetic patients has been examined for evidence of alteration in pancreatic or hepatic activity. Pancreatic enzyme activity was diminished in nearly one-half of the cases. Bile pigment elimination in the duodenal contents was abnormally high in about three-fourths of the cases. In nearly one-third of the cases there were associated enzyme and pigment abnormalties. The greatest alterations in enzyme activity were noted in the lipolytic and proteolytic ferments. These findings are taken to indicate that in diabetes mellitus there is a marked alteration in the external secretory activity of the pancreas and in the hepatic function. The enzyme abnormalities are probably due to associated anatomic and functional changes in the acinar tissue of the pancreas. Undernutrition may play a part in the production of such changes, but it is not the sole cause. Such alterations in pancreatic or liver function may well contribute to the symptomatology of diabetes. It is suggested that the diminution of enzyme activity may result in disturbances due to improper digestion of fat and protein. Undernutrition, of the several variable factors entering

into an uncomplicated case of diabetes, evidently places the greatest strain on the liver, and results in striking bile pigment abnormalities. Undernutrition should therefore be avoided, on account of its undesirable effects on liver and pancreatic function. Efficient insulin therapy, with its associated increase in food intake and improvement of tissue function, seems to be associated with a reduction in pancreatic and hepatic abnormalities. Cases of diabetes complicated by pancreatic disease were found to be associated with an increased frequency of pancreatic enzyme disturbance. Sepsis, gangrene, and pancreatitis seemed to be predominating factors in producing an alteration in bile pigment metabolism. All three patients with hemochromatosis showed a reduction in enzyme activity, but no abnormality in pigment elimination. Acidosis produces a marked disturbance of pancreatic enzyme activity and liver function. The improvement in pancreatic and hepatic function, as measured by changes in the enzyme activity and bile pigment elimination, following recovery from acidosis, is very striking, and illustrates the degree to which acidosis affects all bodily functions. Cholelithiasis, as diagnosed by examination of the duodenal sediment, occurred in 19% of the cases in this series. The sediment findings by which such a diagnosis can be made are characteristic, and have been previously described. In addition, several other patients had histories or operative findings consistent with the diagnosis of gallstones. The average age of this group of cases, constituting 22% of the entire series, was about 51. The authors believe that the existing figures for the incidence of gallstones in diabetes is far too low. It would not be surprising to find that at least one-fifth of all diabetic patients over 40 have an associated cholelithiasis. In adults, cholelithiasis is probably one of the most important etiologic factors in diabetes mellitus. For this reason, it would seem that surgical intervention in all cases of gall-bladder disease, in the absence of other complication, is indicated as a means of preventing the occurrence of diabetes, or of relieving an existing diabetes.—Authors' summary.

The changing diabetic clientele. Joslin (E. P.), Tr. Ass. Am. Physicians (Phila.), 1924, 39, 304-307.

Joslin states that a new race of diabetics has come upon the scene, in that the duration of the diabetes among patients entering the hospital for treatment during 1923 was 5.6 years, 2 years greater than in 1921 and 1922. The duration of the disease among these living diabetics exceeded by a year the entire duration of diabetes among all Joslin's fatal cases up to the year 1914. The diabetics of today are 11 years older than those of a decade ago, and since they represent to an extent a milder type of the disease, this would indicate an increased zeal on the part of the medical profession in the diagnosis of early cases. The prevention of diabetes is as im-

portant as the prevention of an infectious disease. Prophylaxis is possible because it is known to be 15 times as frequent among adults, it is 10 to 20 times as common among the fat, it is 2½ times as common among Jews, and slightly more so among Jewish females. A campaign to eradicate diabetes should therefore yield maximum returns if directed toward its prevention and discovery in adult, fat females, and particularly in Jews. However, a Jewish child is no more prone to diabetes than the child of a Gentile. Insulin has exceeded expectations and coma is relieved far more surely than was the case heretofore. Moreover, the educational value of insulin is of vital importance, there having been promoted among physicians and patients a profound consideration of details in diet and a respect for scientific medicine.—I. B.

Action of insulin on the central nervous system (Zur Wirkung des Insulins auf das Zentralnervensystem). Kleitman (N.) & Magnus (R), Arch. f. d. ges. Physiol. (Berl.), 1924, **205**, 148-154.

For occurrence of convulsions after insulin injections into rabbits (and cats) presence of the medulla oblongata is necessary. Cerebrum, thalami, forepart of middle-brain and labyrinth are unnecessary. The hypoglycemia produces independently (a) stimulation of motor centres in the medulla, followed by convulsions, (b) stepwise paralysis of the position reflexes and certain labyrinth reflexes, though the majority of these remain unaffected, and (c) cessation of breathing.—A. T. C.

Examinations on the manner of effect of insulin. Lundsgaard (C) & Hollböll (S. A.), Ugesk. f. Læger (Copenhagen), 1924, **86**, 591-597; 693.

The authors describe a method (dialysis through certain collodion membranes) of producing clear solutions of glucose to which there can be added non-transparent materials, for instance, blood. They have shown that by adding pure insulin or insulin and fresh blood to solutions of glucose there can be produced a change in polarization of the solution. If blood sugar in normal persons is found in the Gamma form the Beta glucose absorbed through the intestinal tract cannot be changed to Beta in the blood; the conversion is brought about by some extravascular process. It is shown that ordinary Beta glucose is changed into the Gamma form by addition of insulin together with muscular tissue in vitro. The effect of different factors (glucose concentration, amount of insulin, amount of muscular tissue, temperature) in the process is studied quantitatively. The muscular tissue must be fresh; its efficacy disappears in 2 hours. Its activity must therefore be conditioned by vital processes of the cells. By repeated fractional addition of insulin and muscular tissue to the same solution of glucose the concentra-

·tion of the Gamma form can be raised to 76% of the total amount of glucose. The conversion process is reversible,· but only very slowly. Addition of normal gastric juice to a solution containing Gamma glucose does not accelerate the reverse conversion.

—K. H. K.

On the mechanism of insulin action. Mueller (E. F.), Wiener (H. J.) & Wiener (Renee von E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 375-382.

Insulin was injected subcutaneously and intracutaneously in normal human subjects and the fall in blood sugar was studied. It was more rapid following the intracutaneous injection. In rabbits blocking the nerves to the skin area injected abolishes the difference between the results from the two methods. Absorption is slower in the case of the intracutaneous injections, but the fall in blood sugar in these cases begins before the hormone can be effective through the blood, i. e., 20 minutes after injection. The authors believe, therefore, that there is a nervous stimulation from the injected area, probably through the parasympathetic system, which inhibits glycogen formation, thus bringing about an initial fall in blood sugar. Later the direct hormonal effect appears and overshadows this first reduction.—J. C. D.

Five cases of diabetes and coma. I. The effect of three attacks of coma upon tolerance. II. Infection and coma. III. An obscure case of coma. IV. Coma due to cerebral hemorrhage simulating diabetic coma. V. Renal insufficiency simulating diabetic coma. Murphy (W. P.), Med. Clin. N. Am. (Phila.), 1925, **8**, 1517-1528.

Acidosis with coma may have a very acute onset and be precipitated by infections, dietary indiscretions, or lack of proper cooperation in diabetic treatment. The CO_2 combining power of the blood is a more reliable index of the degree of acidosis than the urinary diacetic reaction. It is dangerous to make the diagnosis of diabetic coma in cases without a lowered alkali reserve. There is usually a relatively high red and white blood count in coma cases. The blood changes are probably due to the dehydration, which may be marked in acidosis. The author emphasizes the practical details in the management of cases of diabetes with severe acidosis or in coma.—I. B.

Severe acidosis of diabetes. Musser (J. H., Jr.), Med. Clin. N. Am. (Phila.), 1925, **8**, 775-779.

Tuberculosis does not occur in diabetics more often than in non-diabetics. When the two diseases are associated the problem is serious, and it is more important to treat the diabetes than the tuberculosis. It is especially with the aid of insulin that the patient

may be sufficiently nourished and made sugar free. Intelligent co-operation is a valuable asset.—I. B.

Experimental researches on the pathogenesis of ketosis. Petren (K.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 317-319.

Basing his opinion upon studies carried on during a period of 13 years, the author concludes that it is best to give only a small amount of protein in grave diabetes (1-3 to 1-4 gram per kilo of body weight, or even smaller amounts). On the other hand, there is no danger in giving the amount of fat that corresponds to the requirement of the nutrition. He found such lowering of the protein of the food to be the best way of reducing hyperglycemia and ketosis.—I. B.

Insulin in diabetes requiring surgery. Petty (O. H.) & LeFevre (W. M.), Med. Clin. N. Am. (Phila.), 1925, **8**, 919-930.

A valuable contribution on the subject, with several case histories. Of the 31 diabetes patients operated upon, 7 required foot and leg amputations, and of these there were 3 fatalities. Patients requiring over 70 units of insulin daily possess some complication, probably a focus of infection inhibiting the action of insulin. Removal of the infection enhances the effect of insulin. Surgical technic does not differ from that used in non-diabetic patients. Close co-operation between internist and surgeon is essential in these cases. Preoperative diabetic treatment is either an emergency or a routine procedure, depending upon existing indications. Postoperative diabetic management is likewise of utmost importance. Postoperative acidosis is prevented by the use of carbohydrates, liquids and insulin.—I. B.

Age as a factor in diabetic mortality. Thomason (J. W.), Boston M. & S. J., 1925, **192**, 532-536.

Careful study of statistics leads the author to conclude that in comparing diabetic with general mortality it is manifest that the diabetic mortality reaches two distinct elevations, a peak and a plateau. The peak occurs at the age of fifteen years and is a relative increase, while the second, the plateau, develops between sixty and seventy years of age and is an actual increase. The diabetic mortality curve begins to rise rapidly at from forty-five to fifty years of age, reaching its maximum at eighty years for all four decades and then rapidly falls.—J. C. D.

Results following the extirpation of the pineal gland in newly hatched chicks. Badertscher (J. A.), Anat. Record (Phila.), 1924, **28**, 177-197.

The operation was performed on White Leghorn chicks 4-5

days after hatching. The gland was removed completely from 5 cockerels and 6 ·hens and only partially removed from 5 cockerels and 9 hens. The latter served as traumatized controls; 9 cockerels and 16 hens served as normal controls. The chickens were weighed at regular intervals and observations made on the development of the primary and secondary sex characters (crowing, comb, sexual instinct). Growth curves were constructed from the average rate of growth for each group. At the termination of the experiments the testicles and combs of the males of all groups were weighed for comparison. Badertscher believes that his results can all be interpreted as negative. His results are contradictory to the prevailing notion that pineal gland deficiency results in a precocious somatic and sexual maturity.—W. J. A.

Exophthalmic goiter in children. Burnet (J.), Internat. Clin. (Phila.), 1925, **1**, S. 35, 94-96.

A brief discussion of the etiology of exophthalmic goiter in children, and the report of a case in a female child of 9 who apparently recovered under treatment consisting essentially of the administration of tincture of iodine.—I. B.

Lymphoid hyperplasia in the thyroid gland. Caldwell (G. T.), South. M. J. (Birmingham), 1925, **18**, 177-180.

This is a condition which has been previously described. It is known in its extreme form as Riedel's struma, which is characterized by a markedly increased density of the gland. Twenty-nine cases have been seen in 5 years in general hospital practice, so it is more frequent than is usually stated. All were in women. Three only were of the extreme type. The condition was not regularly associated with infections in other parts of the body.—J. C. D.

Surgical aspects of goiter. Frazier (C. H.), Atlantic M. J. (Harrisburg), 1925, **28**, 376-385.

Except from the standpoint of preoperative preparation, the differentiation between toxic adenoma and exophthalmic goiter is, insofar as the successful management is concerned, a matter of little moment. Basal metabolism determinations are important. Frazier does not agree with Crile that the metabolic rate is not a guide to operability. He is thoroughly convinced that surgical therapy is the most effective means of arresting the symptoms of toxic goiter. He quotes from his own records, deduced from reports on questionnaires sent out to patients, in which 27% of his patients are reported as being "entirely well" and 73% as "improved." The correction of serious cardiac disturbances is an important preoperative procedure. Digitalization may be resorted to and may be continued during the first few postoperative days. The fractional

method of operating in bad risk cases is essential. The psychological factor in the preparation of the patient is a vital therapeutic procedure. A persistent thymus should receive x-ray treatment for 2 weeks before operation. There is always danger of damage to the recurrent laryngeal nerves. This can be overcome by grasping the vessels at the inferior pole close to the capsule, and by the avoidance of resection of the lobe on its mesial aspect below the level of· the trachea. Paralysis of the recurrent laryngeal nerve not only results in dyspnea, aphonia, and in the pulmonary complication of the operation, but occasionally in death on the operating table. Transfusion by the citrate method following operation adds to the safety of the patient. If there is perfect teamwork on the part of the operating surgeon and his assistants the death rate appears negligible. There was no mortality associated with the series of 185 operations reported by Frazier.—I. B.

Influence of the thyroid gland on the increased heat production occurring during pergnancy and lactation. Marine (D.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 180-190.

As a result of observations on rabbits, the author concludes that there is probably an increase in the metabolism of the pregnant woman that cannot be accounted for entirely on the basis of the active protoplasmic mass of the fetus; that the heat production during lactation remains elevated, though this increase is less than half of that present before parturition, and that the maternal thyroid, through its increased functional activity, increases heat production during pregnancy and lactation. Marine believes that these findings partly explain why pregnancy and lactation constitute one of the three important periods in life when simple goiter develops.
—I. B.

Iodine therapy in toxic goiter. Mason (E. H.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 167-179.

Basing his remarks on data of 8 detailed case histories, the author believes that in exophthalmic goiter iodine administration is an important step in therapeusis, especially in preoperative management.—I. B.

Goiter in the intermountain region of Utah. Middleton (G. W.), J. Am. M. Ass. (Chicago), 1925, **84**, 1172-1173.

The larger phase of the goiter problem, and the one that may prove to be most significant in the future, Middleton says, is the relative iodin deficiency in the various geological strata that form the catchment basins and water sheds of the streams. If this were determined in any given section, one could at a glance estimate the probable goiter incidence and the extent of prophylactic measures

necessary to meet the situation. Theoretically, all volcanic or granitic sections of country should have a relatively large percentage of goiter incidence. Whether this is the case remains to be proved, but in the data available in the intermountain region of Utah there is at least a marked indication in that direction. Thus, in the town of St. George, in Southern Utah, with a population of more than · 3,000, goiter was quite unusual for more than half a century, from the time of its founding until a water system was installed and the water from the Pine Valley Mountains brought in. Pine Valley Mountains are almost entirely igneous, and the volatile iodin no doubt escaped at the time of their extrusion. Since the advent of the new water supply, many people have developed goiter, and what was for a long time a comparatively immune district has now been added to the large endemic section of Southern Utah. In the Virgin Valley, which is a part of this section, fully 75% of the adult women have goiter. It is here, in these isolated mountain gorges, that one encounters enormous thyroid growths, which are allowed to progress unchallenged until they assume maximal dimensions. It seems to be well established by the statewide survey now in progress that towns which enjoyed considerable immunity from goiter while they used well water, and water from the surface springs are taking on a marked increase of goiter incidence since they installed water systems, and are getting their water supply from mountain springs up near the melting snows. During the past 3 years Middleton has treated 333 cases of the various forms of goiter, not including hypothyroidism or the inflammatory conditions. One hundred and fifty-six thyroidectomies were performed with 2 fatalities, a mortality of 1.3%. Seventy-three percent of these patients were toxic, and many of them extremely toxic. One of these fatalities was due to tracheal obstruction, and one patient was so toxic that she showed no improvement after months of rest and medical treatment, and thyroidectomy was undertaken as a last resort. Middleton believes that rest in bed with abundance of fluids, and the use of compound solution of iodin in the hyperplastic cases are the most important preparatory measures. Except in cases with broken compensation, preoperative digitalization has been of little value. Calcium carbonate is given to prevent tetany. The condition described as hypoglycemia has been encountered five or six times. Urinalysis showed much acetone and diacetic acid. The relief from intravenous glucose was striking.—A. M. A.

Iodine in the treatment of goiter. Plummer (W. A.), Med. Clin. N. Am. (Phila.), 1925, 8, 1145-1151.

In goiters containing adenomatous tissue, iodine administration, especially after the adolescence, may engender hyperthyroidism. Even the minute quantities of iodine present in iodized salt or in the water supply may have the same effect. Thyroid

administration under similar conditions is not so likely to yield
hyperthyroidism, although adenomatous tissue is seldom reduced by
this substance. In the Mayo Clinic, 10 minims of Lugol's solution
are administered 3 times a day for at least 7 days prior to thy-
roidectomy. In patients with crisis or near crisis, 50 minims are
given during the first 2 or 3 hours by mouth or by rectum, depend-
ing upon conditions. If the patient is in crisis 50 minims are ad-
ministered again during the following forenoon. Patients with post-
operative recurrences are given 10 minims daily over an indefinite
period with intervals of cessation of the drug and readministration
if necessary. The operative mortality with the use of Lugol's solu-
tion has been reduced 2% or more.—I. B.

**Syphilis of the thyroid gland, with special reference to exophthalmic
goiter.** Schulmann (E.), Internat. Clin. (Phila.), 1924, 4, S. 34,
126-136.

A useful survey of syphilis as an etiological factor in exoph-
thalmic goiter. Ewald's theory that the thyroid enjoys a kind of
immunity to syphilis on account of its iodine content can no longer
be maintained. Following a brief discussion on syphilis as pro-
ductive of myxedematous states, the author quotes Pierre Marie
and others to substantiate his views that lues is not an unknown
causal factor in exophthalmic goiter. Two types of the tertiary
syphilis of the thyroid gland are recognized: (1) gummatous thy-
roiditis, which is the most common, and (2) interstitial or sclero-
gummatous thyroiditis. Schulmann presents 3 illustrative case his-
tories. Syphilitic exophthalmic goiter usually develops without any
special predisposition, and one does not ordinarily find those neuro-
pathic taints upon which much stress is laid in the usual forms of
the Basedowian syndrome. The time elapsing between the inci-
dence of syphilis and the development of exophthalmic goiter varies
greatly. Sometimes the symptoms may develop during the second-
ary phase of the syphilis, at other times during the tertiary phase.
In one case of the author's, exophthalmic goiter developed 23 years
after the onset of syphilis. Occasionally the Basedowian syndrome
may appear during the evolution of tabes dorsalis, thus showing the
simultaneous tardy influence of the spirachetae, both on the pos-
terior columns of the spinal cord and the endocrine glands. The
symptomatology of this type of exophthalmic goiter does not differ
from the usual form. The syndrome usually develops progressively
and in many instances is for a considerable period of time unnoticed
by the patient. Specific treatment applied to the syndrome result-
ing from lues is frequently quite successful and is a criterion of the
highest order in the discrimination between this and the ordinary
types of exophthalmic goiter. —I. B.

Liver injury in thyrotoxicosis as evidenced by decreased functional efficiency. Warfield (L. M.) & Youmans (J. B.), Tr. Ass. Am. Physicians (Phila.), 1924, **39**, 130-135.

Injury to the liver may occur in extremely severe cases of thyrotoxicosis, and jaundice has been regarded as a grave prognostic sign. It has recently been suggested that diminished sugar tolerance occurring in thyrotoxicosis may be due to liver damage. As the result of a combined study of the functional efficiency of the liver and of the glucose tolerance in cases of thyrotoxicosis, the authors find that injury to the liver occurs in a surprisingly large number of instances. Of the 30 cases studied, 12 showed evidence of injury to the liver according to the phenoltetrachlorphthalein test of Rosenthal. Jaundice occurred in 3 instances, and was associated with the most marked evidence of liver damage observed. Hepatic damage bears no constant relationship to the sugar tolerance, basal metabolic rate, loss of body weight, or other known factors concerned in this disease.—I. B.

PRECOCIOUS MENSTRUATION: OBSERVATIONS ON TWO CASES OF PUBERTAS PRECOX[*]

HOMER WHEELON, M.D.
SEATTLE, WASH.

The outstanding clinical manifestations of pubertas precox in the female are menstruation with associated development and early maturity of the body as a whole.

The average age for the establishment of menstruation in normal girls is between the thirteenth and fourteenth years. According to certain German statistics, menstruation occurs between the ages of 8 and 12 in 3.5 per cent of all cases. Lenz (1913) contends that menstruation should not be looked upon as precocious unless occurring under the age of 8 years. Novak (1921) says: "If menstruation begins and recurs regularly in a girl of less than 9 years of age, in this country (United States), it must be looked upon as precocious."

Lenz (1913) collected 130 cases of precocious menstruation occurring prior to the seventh year. Of this number 43 began to menstruate during the first year of life and 6 had their initial flow within the first month. In some cases menstruation continues regularly, save during pregnancy or lactation; however, this is the exception rather than the rule. The duration of the

flow varies from 2 to 6 days, a variation comparable to that observed in normal adult women. These patients frequently complain of symptoms like those experienced by adult women at the menstrual period.

Conception is not infrequent in cases of sexual precocity. Lenz (1913) collected 10 cases of childbirth in girls before the age of 12 years.

Early development and maturity of the body as a whole usually occurs concomitantly with the appearance of precocious menstruation. Lucas (1888) reports the case of a girl who at the age of 7 years showed all of the signs of genitosomatic maturity and early menstruation. A tumor of the ovary was diagnosed and removed, following which all signs of adolescence and menstruation disappeared. The 7 year old patient reported by Brohl (1897) showed the development of a mature woman. In this instance, following the removal of a cystic ovary, menstruation ceased. The 5 year old patient of Harris (1917) ceased menstruating and regained her childish features following the removal of a carcinomatous ovarian teratoma. The 6 year old patient of Riedl (1904) had a uterus the size of that of a normal girl of 17 years. Removal of an ovarian sarcoma was followed by cessation of menstruation. The 2½ year old girl reported by Klein (1899) showed development of the vulva equal to that of a girl of 14 years. Stocker, quoted by Falta (1915), describes twin sisters, of whom one had been larger since birth. In the first, menstruation began before the end of the first year. The flow occurred regularly every 4 weeks, lasting 3 days. At 8 she had the size and appearance of a girl of 12 years; she was 139 cm. tall and weighed 34.75 kg., while the twin sister was 121 cm. tall and weighed 20 kg.

Osseous development usually parallels that of the sexual characters in cases of precocious menstruation. The bones are larger than normal for the age and ossification is further advanced than would be expected. The epiphyses unite early with the shafts, or are separated by only thin discs of cartilage. The pelvis in many cases resembles that of the fully developed woman. A case is reported by Wolff (1911) of a girl who at the age of 4 years had an osseous development equal to that of a normal girl of 10 years. Krabbe (1919) reported the case of

a girl seen at 13½ years of age. This patient began to menstruate during her first year and continued regularly every 4 weeks without interruption. Sex signs appeared early, the hips and thighs having always been prominent. She grew rapidly until the age of 7 years. Thereafter she did not grow in height and at the time of examination her lower limbs were strikingly short in relation to her trunk. The x-ray examination showed all the epiphyseal fissures of the upper and lower limbs completely grown together.

The precocious development of sex characters and somatic structures does not appear to cause a similar early appearance of psychic development. Leiner (1920), for instance, states that mental traits and habits are in no way precocious: "In fact, the subjects are of a low mental type. They speak, play and act in accordance with their true age. They learn well at school, but they show no 'old fashioned' way of thinking." Krabbe (1919), in discussing this point, asserts that in cases of "pubertas precox as in infantilism there may be a disassociation between somatic and psychic evolution. There are some cases in which they are parallel, but others where the psychic evolution is normal, while the somatic is either advanced or retarded."

Williams, quoted by Bell (1916), collected 11 cases in which ovarian neoplasms were associated with sexual precocity in female children. However, as pointed out by Leiner (1920), we should not draw the conclusion that all ovarian tumors in young girls necessarily lead to sexual precocity. Neither should it be assumed that all cases of precocious menstruation are the result of ovarian tumor masses. On the other hand, Novak (1921) asserts that "very few autopsies are recorded in cases of precocious menstruation in which there was no tumor present either in the ovaries or in the other internal secretory glands."

Undoubtedly many women are living who were subjects of pubertas precox and who will live to old age without the condition ever having been recognized. It is conceivable, as pointed out by Krabbe (1919), that early menstruation associated with precocious sex and somatic development "may be caused by an abnormally early function of the internal secretion of the ovaries, an early function which is not caused by a tumor, but is parallel to hypersecretion of the thyroid gland in Graves'

disease.'' A somewhat similar interpretation is given by Lespinasse (1922) for the appearance of pubertas precox in boys.

PRESENTATION OF CASES

Case No. 1, Nov. 29, 1924. Miss M. M., age 14 years and 11 months, white, student.

Complaints: Nervousness, over weight, shortness of stature and acne.

Family History: The father is 38 years old, 68½ inches tall and weighs 196 pounds. The mother is 39 years old, 65 inches tall and weighs 133 pounds. She states that her growth ceased between the ages of 10 and 15 years and that she grew in height after the age of 21. Her first menstrual flow occurred when she was 15 years old. The second period did not appear until the age of 19. She married at the age of 20, at which time she weighed 95 pounds, and has been pregnant 18 times. Three pregnancies lasted 6 months; the remainder, save two deliveries, terminated before the third month. She has been told that her child's condition resulted because of vaginal hemorrhages during gestation. A maternal uncle is a hunchback and 2 cousins are very short. There is no ascertainable history of congenital deformity, maldevelopment, insanity or feeble mindedness on either side of the family.

Clinical History: The patient was delivered at full term after a prolonged labor and weighed 9 pounds. She was breast fed. During her sixth month she had 10 convulsions. She was talking at 12 months and beginning to walk at 14 months.

The patient had a vaginal discharge of blood at 18 months. This was repeated every 90 days until about the age of 5 years. After this the periods occurred every 60 days until the age of 10, from which time they have appeared every 27 to 30 days. The menstrual flow has been variable in amount and duration. Until the age of 12 the periods were accompanied by excruciating pelvic cramps; head- or back-aches were not present. Premenstrual irritability has been of common occurrence. Masturbation was practiced a great deal during the third year.

Pubic and axillary hair appeared at the age of 5 years. Hair has never appeared on the face, trunk or abdomen. The voice became heavy with the appearance of the pubic hair and continued so until the age of 9, since which time it has become more nearly normal. The breasts enlarged rapidly during the fifth year and "at 9 she had the features of a completely developed small woman."

"M. was a handsome and healthy baby." She began to grow rapidly during her fifth year and continued to do so until the age of 9, since which time she has grown but little, if at all. During the period

of growth she required but little sleep and showed a high degree of interest in the affairs of others. Since the age of 9 she has taken on considerable weight, gradually lost interest in her surroundings and now requires considerable sleep.

Dizzy spells and stupor have been annoying symptoms for the past 3 years. She describes her sensations as follows: "The head feels like it is opened in the middle." Associated disturbances have never accompanied these "head attacks."

The patient has always been retiring, suspicious and afraid of people. She played with her dolls until a year ago. She has never shown anything but a healthy dislike for boys and only a moderate interest in girls. Her dislike for both boys and girls is partially explained because of their teasing her about her over-development. She is apparently somewhat conversant with matters of sex. According to her mother, the patient has never shown any signs of sex interest and is not affectionate. She has always been wilful, stubborn and hard to manage. She has been extremely nervous since one year of age. Her disposition has been decidedly more intractable of late. She starves herself in an effort to keep down her weight.

The patient did not enter school until the age of 9 because of nervousness. She has slowly made her grades and is now attempting high school work. Because of her poor school work she was seen on Jan. 9, 1920, by Dr. Stevenson Smith of the Psychology Department of the University of Washington. A part of Dr. Smith's report follows: "In response to mental tests, she is superior to approximately 28 per cent of children of her age. It appears that her precocious physical development and her mother's training, which has kept this always before the child's mind, has played some part in the development of the temperamental condition which is so obvious."

The patient as a child had several attacks of bloody dysentery. At the age of 9 years she had mumps, whooping cough, measles and scarlet fever. She had a second attack of measles at 11 years. She had chicken pox as a baby. Her tonsils and adenoids were removed at the age of 10 years. Acne has been present for several years.

Present Status: The menstrual periods are regular and associated at times with pelvic cramps. "Head attacks" are rather frequent. She is very irritable, stubborn and restless.

Physical Examinations: The patient is of a pudgy build and has the appearance of an overdeveloped and matured woman. The torso length is noticeably greater than the lower measurement. The neck is short and stout. The thighs are thick as also are the forelegs. There is moderate and general fat padding. The musculature is well developed and firm. The posture is good save for a slight droop of the shoulders (Fig. 1).

Figure 1. Outline drawing from projected photographic negatives of subject No. 1. Note the disproportion between the torso and lower lengths, largeness of the breasts and thickness of the thighs and forelegs.

Measurements:

Weight	48.6 kg.	107 pounds
Height ....:....................	146.0 cm.	57⅜ inches
Span of arms....................	141.5 cm.	55⅝ inches
Torso length....................	79.5 cm.	31¼ inches
Plantar-symphyseal length.........	66.5 cm.	26⅛ inches
Head circumference—antero-posterior	54.5 cm.	21⅜ inches
Head circumference over vortex......	34.5 cm.	13½ inches
Interpupillary distance	5.5 cm.	2⅛ inches
Neck circumference.................	31.5 cm.	12⅜ inches
Shoulder circumference............	88.0 cm.	34⅝ inches
Axillary circumference	79.0 cm.	31⅛ inches
Bust circumference.................	76.5 cm.	30⅛ inches
Waist circumference at navel........	65.5 cm.	25¾ inches
Crest of ilium circumference	79.5 cm.	31¼ inches
Trochanter circumference...........	89.5 cm.	35¼ inches
Elbow (Rt.) circumference..........	23.0 cm.	9 inches
Wrist (Rt.) circumference..........	15.5 cm.	6⅛ inches
Knee (Rt.) circumference...........	36.0 cm.	14⅛ inches
Ankle (Rt.) circumference..........	22.5 cm.	8⅞ inches

The skin is dry, pliable and has a good color. The hands, feet and axillae are moist. The finger and toe nails are well formed. The head hair is abundant, black in color, of fine texture, oily and has a high anterior attachment. The eyebrows meet to form a nasal brow. The axillae contain a luxuriant growth of dark hair. Pubic hair is abundant and of feminine distribution. There is a definite growth of hair over the forelegs and to a less degree over the forearms. The face and trunk are free from hair.

The cheek bones are prominent, the nose is pudgy and the lips are quite thick. The voice is harsh and low pitched; speech is normal. The teeth are all present save the third molars and have a dirty yellow color. The lower set are wired for correction of alignment.

The thyroid gland is not palpable. The abdomen, chest and heart show nothing abnormal on percussion and auscultation. The blood pressure is 130/70; the pulse rate 96; the buccal temperature 98.2° F. The arteries are soft and the veins small and well imbedded.

The breasts are well developed and firm. The left breast is noticeably larger than the right. The labia majora and minora are well developed. The vaginal inlet and the cervix are small. The body of the uterus and the adenexa could not be completely examined because of vaginismus and abdominal rigidity.

The neuro-muscular apparatus is entirely negative for pathological findings. Sensibility is normal. Careful ocular examinations made by Dr. Walter K. Seelye were negative save for the finding of reduced visual acuity, a condition not accounted for by any objective findings.

Laboratory Examinations: Blood: Wasserman reaction negative; hemoglobin, 97 per cent (Dare); red cell count, 4,176,000; white cell count, 13,000 one hour after lunch; differential count: polymorphonuclear cells, 58; small lymphocytes, 12; large lymphocytes, 27; eosinophile, 2; blood sugar, 120 mg. per 100 cc. of blood. The urine and vaginal smears are negative. The basal metabolic rate is +14 per cent; a second reading could not be secured.

X-ray Examinations: Epiphyseal lines are not demonstrable in the bones of the extremities. The frontal sinuses are extensive. There is marked irregularity in the density of the frontal bone. The third molars have not erupted. There is marked forward projection of the upper and lower frontal teeth. The sella turcica is small and the clinoids show no evidence of erosion. There are no shadows in the region of the pineal body.

Diagnosis: 1. Genitosomatic: Evolutio precox corporis and resultant dwarfism. 2. Psychic: Mentally inferior to approximately 75 per cent of individuals of her age. 3. Reduced visual acuity unaccounted for by objective findings. 4. Acne simplex.

Case No. 2, Jan. 1, 1925. Miss C. M., age 18 years, white, student.

Complaints: Painful menstruation, headache, pains in the legs and back and marked deposition of fat over the trochanteric regions.

Family History: The patient's mother began to menstruate at the age of 12 years and attained her present height of 66 inches prior to the age of 14 years. Her periods were not regular until after the birth of her first child. An only sister of the patient began to menstruate at the age of 14 years. The family history does not disclose insanity, tuberculosis, congenital malformations or growth disturbances.

Past History: The patient was delivered normally at full term and weighed 6 pounds. She was walking and talking at 14 months. The deciduous teeth were erupted "at the usual time." She weighed 19 pounds on her first birthday. During her second summer she contracted cholera infantum, measles and chicken pox. As a result of this she weighed but 21 pounds on her second birthday. "Her hair became thin and straggly," she was puny, sickly and poorly nourished and continued to have intestinal trouble each summer until the age of 5 years. At the time she started to school she began to increase in weight; her hair began to grow rapidly and became glossy. Moderately severe gastrointestinal disturbances appeared again during her seventh year and markedly interfered with her school work.

She injured her sacrum and coccyx when 8 years of age and one year later took treatment for "deformity at the tip of the backbone." Shortly following this injury she began to take on weight and grew rapidly in height. Growth continued rapidly until the age of 13 years, since which time she has continued to take on weight, espe-

cially about the thighs. A few months preceding the rapid bodily development, that is, during the eighth year, the patient had a severe attack of pain in the right iliac fossa associated with high fever, nausea and vomiting. She experienced a similar attack at the age of 15 years, at which time the condition was diagnosed as acute appendicitis.

The breasts and external genitalia began to develop rapidly during the summer prior to her ninth birthday. Pubic and axillary hair appeared during her eighth year and "she was fat all over." At the age of 9 years and one month she began to menstruate. The initial flow was not preceded by prodromal symptoms, but was associated with severe headaches and pelvic cramps. Subsequent periods, which appeared regularly, were preceded by severe headaches and cramps and accompanied by backache and legache. The average duration of the flow has been 3 days; the amount of the flow has always been moderate. The headaches, which were of a migraninous nature, usually ceased with the establishment of the flow. At the age of 11 years the voice became heavier and had the pitch and timbre of an adult voice.

The patient weighed 133 pounds at the age of 12 years. Since the age of 13 years, at which time she attained her present height, she has developed abnormally about the hips, especially over the thighs.

The patient had whooping cough when 3 years old, mumps at 7 and at 10 an attack of pleurisy. At 13 years she had several attacks of tonsilitis and developed a "weak heart." The tonsils and adenoids were removed the same year. At 14 years she had a rather severe attack of influenza and the heart developed a murmur. She has never had convulsions or fainting spells. The eyes have been sensitive to light since early childhood. She has made her school grades easily.

Present Status: Premenstrual headaches have been getting progressively worse for the past 5 months. They usually begin from one to five days before establishment of the flow and are located along the posterior part of the neck, at the base of the skull and behind the eyeballs. These headaches usually appear in the morning and are associated with slight nausea. At times vision is blurred; however, blindness or diplopia have never occurred. The onset of the period of headaches is usually preceded by a few days of marked somnolence, general weakness and fatigability. Establishment of the menstrual flow is followed by complete relief from headache.

The menstrual flow lasts on the average only three days and is "only average in amount." Because of the severity of pelvic cramps, backache and pains in her hips and legs during the flow, she is forced to go to bed and at times requires opiates. For the last three months she has experienced heavy bearing-down pains, backache and pains in the legs, especially the right, following cessation of the flow and during the intermenstrual period. She is now subject to severe

cramps and drawing pains in the legs. These cramps and the backache are decidedly more pronounced on the right side. The right leg goes to sleep a great deal.

Considerable belching after meals and obstinate constipation have been noticed since the appearance of the premenstrual headaches.

Figure 2. Outline drawing from projected photographic negatives of subject No. 2. Note the degree of fat padding over the trochanteric regions.

Sleep is restless because of the backache, which is relieved only by placing her arms under the small of the back. Her strength is excellent; however, she is restricted in her activities because of the constant distress in the back and legs. She wears glasses to read with.

The patient is emotionally sensitive and very particular in the choice of her friends. Apparently members of the opposite sex hold

very little interest for her inasmuch as she has "never had a love affair." She complains of dreaming a great deal, becomes frightened in her dreams and talks considerably in her sleep.

Physical Examinations: The patient shows a marked disproportion of fat distribution, there being an excessive accumulation of adipose tissue over the trochanteric regions (Fig. 2). The posture is good. There is some falling of the pedal arches.

Measurements:

Weight, without clothes	71.6 kg.	157	pounds
Height	162.7 cm.	64.0	inches
Span of arms	166.0 cm.	65⅜	inches
Torso length	78.5 cm.	30⅞	inches
Plantar-symphyseal length	84.2 cm.	33⅛	inches
Circumference of head over vertex	36.3 cm.	14¼	inches
Antero-posterior circumference of head	55.6 cm.	21⅞	inches
Interpupillary distance	5.5 cm.	2⅛	inches
Neck circumference	34.0 cm.	13¼	inches
Shoulder circumference	95.0 cm.	37⅜	inches
Axillary circumference	81.0 cm.	31⅞	inches
Circumference of bust	84.0 cm.	33	inches
Circumference at level of navel	69.0 cm.	27⅛	inches
Circumference at crest of ilium	93.0 cm.	36⅝	inches
Circumference at level of symphisis	106.0 cm.	41¾	inches
Circumference over trochanter	122.0 cm.	48	inches
Circumference of right elbow	24.6 cm.	9½	inches
Circumference of right wrist	16.0 cm.	6¼	inches
Circumference of right knee	43.0 cm.	17⅛	inches
Shoe size			No. 6½
Glove size			No. 6½

The skin is soft, pliable, moist and has an excellent color. The hands and feet are livid and moist. The cheeks are florid. Hair development is luxuriant and of typical feminine distribution. Hair is quite prominent on the forearms and legs. The hair follicles on the forelegs are large and cause the skin to feel rough to the touch.

The teeth are crowded, in good alignment and have a clear bluish color. The thyroid gland is palpable and soft.

The blood pressure is 130/82. The pulse is regular but has a high rate, 96 per minute. The heart and lungs are negative upon percussion and auscultation.

There are no disturbances of the neuromuscular apparatus or of the sensibilities.

The mammary glands are well developed. The labia majora and minora are well developed. The uterus is of moderate size and freely movable.

There is considerable tenderness over the right lower quadrant of the abdomen. Pressure over the sacral joint causes considerable distress and pressure over the right hip joint causes pain throughout the entire right leg.

Laboratory Examinations: Blood: Wasserman reaction negative; blood sugar, 130 mg. per 100 cc. blood; hemaglobin, 95 per cent (Dare); red cell count, 4,944,000; white cell count, 7,000; differential count: polymorphonuclear cells, 59; small lymphocytes, 28; large lymphocytes, 13. The urine contains a faint trace of albumin. The kidney function test gives a return of 70 per cent of the dye along with an output of 550 cc. of urine in 2 hours and 15 minutes. The basal metabolic rate is +12 per cent.

Figure 3. Outline drawing of x-ray plates of the right hand of subjects No. 1 (A) and No. 2 (B). Note the differences in size and general structure of the two hands. The epiphyses in each instance are completely closed.

X-ray Examination: The epiphyses of the long bones and those of the hands and feet are closed, as are those of the crest of the ilium. The frontal sinuses are very small. The sinuses are clear. The sella turcica is large; the posterior clinoids show some haziness of outline. The plate of the lumbar and pelvic regions shows no bony abnormality. The pelvis is typically feminine in structure.

Diagnoses: 1. Genitosomatic: Pubertas precox; dysmenorrhea

and trochanteric fat padding. 2. Chronic appendicitis and consti-
pation. 3. Fallen pedal arches. 4. Acne simplex.

Operation: March 26, 1925. The stomach, gall bladder and
liver are normal. The duodenum is large but free from adhesions
and congenital bands. The colon contains much fecal matter. The
cecum and terminal ilium are freely movable. The appendix occu-
pies a retroperitoneal position and is free from adhesions. Two con-
cretions occupy the lumen of the appendix. The right kidney can be
moved about 5 cm.; the left 2 cm. The kidney borders are smooth
and even. No masses can be palpated in the suprarenal bodies.

The uterus is of moderate size and quite soft. The fallopian
tubes are small and their fimbriated ends normal in appearance. The
right ovary is of normal size and contains a corpus luteum of recent
origin at the upper pole; the lower pole is decidedly sclerotic. The
left ovary is very small, sclerotic and has the appearance of a senile
organ.

Figure 4. Outline drawing of x-ray plates of the right knee of subjects
No. 1 (A) and No. 2 (B). The epiphyses in each instance are closed.

DISCUSSION

It is probable that the evolution of precocious puberty
depends on the gonads; that is, hypergenitalism may be looked
upon as the causative factor in the establishment of functional
early puberty. However, the premature development of sex
and sex characters has been observed associated with pathologi-
cal processes in organs of internal secretion other than those
of the gonads. Such associations are so constant that definite
clinical syndromes are described as the result of tumor forma-

tions not only in the gonads but also in the pineal body and suprarenal glands. The precocious appearance of sex and sex characters also has been observed in the absence of demonstrable disorders of these various organs.

The appearance of sex characters in the preadolescent female similar to those which appear in the male at puberty, that is, heterosexual characters, and the precocious appearance of masculine characters and virilism in the preadolescent male, appear constantly as the result of tumors of the adenomatous type (hypernephromata) in the suprarenal cortex. Clinically such cases are described as virilismus when occurring in the female and pubertas precox virilis when present in the male. Such patients should not be classed specifically as cases of pubertas precox for the reason that they are not "functionally capable of generation"; the girls show infantile development of the breasts and genital organs and they do not menstruate, and the boys are said not to produce spermatozoa. Tumors of the suprarenal cortex associated with developmental anomalies of the sex characters appear approximately five times more often in the female than in the male.

Tumors of the pineal body, usually of the teratomatous type, appearing in the preadolescent individual, have been observed associated with the precocious appearance of sex characters and bodily overgrowth. The pineal-gonad syndrome frequently described as macrogenitosomia precox appears more often in the male than in the female; indeed, it was formerly believed that such a condition exists only in the male.

At the present time precocious menstruation is considered under one of three forms depending upon the degree of associated somatic development: 1. *Menstruatio precox*, or the discharge of blood at regular intervals from the generative tract; 2. *Pubertas precox*, or that complex of anatomical and physiological changes in the external and internal generative organs of girls characterized by certain changes in the breasts, the distribution of hair, etc., together with the appearance of certain periodic processes of which menstruation is the most important: 3, *Evolutio precox corporis*, or that array of symptoms associated with an accelerated development of the reproductive system, together with a premature stimulation of the bodily growth.

The latter shows itself in an increase in the size as well as the weight of the body, an accelerated growth of the entire skeleton, and a premature ossification of the epiphyseal cartilages (Novak, 1921).

A diagnosis of evolutio precox corporis is warranted in the first case in that sexual and somatic maturity appeared much earlier than in the average girl. Menstruation, although established in this case at the age of 18 months, was not regular in appearance until the tenth year or following the time of cessation of growth. In fact, this case may be looked upon as one of menstruatio precox up to the age of 5 years. During the fifth year there appeared pelvic and axillary hair, enlargement of the breasts, deepening of the voice and the beginning of rapid growth which continued until the ninth year. Such an association of developmental phenomena together with the fact that the status of the osseous system at the age of 14 years and 11 months is equal to that of the average 18 year old girl sufficiently fulfills the requirements of the diagnosis given. In addition there is the low degree of mental development described by Leiner (1920) as usual in such cases.

Puberty in its entirety as seen in the normal girl is not established in the present case, in that libido has not appeared. A further lack of proof of complete puberty is the inability to know whether or not the patient is functionally capable of generation. The appearance of menstruation, however, is strong presumptive evidence of ovarian maturity.

The possibility of suprarenal disturbances may be dismissed as unlikely. The typical distribution of hair, the absence of pigmented areas of the skin, the marked development of the breasts, the absence of hypertrophy of the clitoris and the presence of menstruation constitute sufficient evidence for such a conclusion.

Evidence of pineal involvement is entirely lacking. There is no evidence of hydrocephalus, brain tumor or eye muscle disturbances, all of which are present in the pineal-gonad syndrome.

The shortness of stature differs markedly from that seen in pituitary and thyroidal disturbances in that the epiphyseal lines are completely closed. The patient's measurements are of the infantile type in that the torso is longer (13 cm.) than the

plantar-symphyseal length, and the spread of the arms less (4.5 cm.) than the height. Such proportions are quite the opposite of those observed in cases of eunuchoidism or gigantism.

Absolute proof of the gonadal origin of pubertas precox in this case is not available, neither is there definite proof of the absence of lesions in the suprarenal cortex or pineal body. Specific pathological evidence is wanting; however, the clinical picture is such as to warrant the diagnosis given.

The second case is diagnosed as one of pubertas precox. Menstruation, in this instance, was established at an age (nine years and one month) that might not be considered as precocious for the appearance of sexual characters. However, the definite series of developmental changes occurring during the eighth year are indicative of both somatic and sexual precocity. These developmental changes appeared suddenly in an individual who, up to that time, had been a puny child. A peculiar series of events antedated the bodily changes; namely, a fall which gave rise to considerable pain in the region of the sacrum for at least one year and an attack of acute appendicitis. Following these she took on weight and began to grow rapidly. Growth continued until the thirteenth year, at which time she attained her present height of 162.7 cm. She was "fat all over" at 9 years and at 12 she weighed 133 pounds. The breasts developed rapidly and hair appeared in the axillae and on the mons veneris during the eighth year. The voice became heavier at the age of 11 years.

The initial menstrual flow occurred one month after her ninth birthday. Later the periods were preceded by prodromal symptoms and accompanied by much distress. Menstruation since its onset has occurred regularly each month. Quite the opposite condition occurred in the first patient.

The development of the generative organs, the distribution of hair, the presence of menstruation, and the lack of intracranial symptoms, in this case, are such as to rule out the likelihood of pathological processes in the suprarenal cortex or pineal body. Further, it was possible to prove the absence of masses in the suprarenal bodies and ovaries during an operation for the removal of the appendix. As for the ovaries, there

appeared to be a high degree of fibrosis (sclerosis) rather than the presence of irritating masses.

Nothing definite is known concerning the time of closure of the epiphyses for the reason that studies on this point were first made at a time when the epiphyses are normally closed. However, there is no evidence of dwarfism. The body proportions differ materially from those of the first patient; the torso length is less (5.7 cm.) than the plantar-symphyseal length and the spread greater (3.3 cm.) than the height. These proportions are eunuchoidal in character. Because of these findings we may assume that the epiphyses were not prematurely closed; at least they were not closed until the bodily proportions had attained definite noninfantile proportions.

To judge from reported cases of pubertas precox, obesity is of common occurrence; however, obesity of specific regions has not been consistently reported. Krabbe (1919) speaks of his subject as always having been wide through the hips and thighs. The second subject presented was fat all over at the time she began to menstruate and continued heavy throughout her growth period. Following attainment of her present height the general obesity disappeared and the localized trochanteric fat padding became prominent. This accumulation of fat over the tronchanters continued to increase until at the time of examination she measured 27 cm. more around the trochanters than around the shoulders.

Because of the eunuchoidal nature of the osseous development and the peculiar distribution of fat we are led to assume the possibility of a hypogonadal condition in spite of the early appearance of menstruation and rapid bodily growth. The severe and persistent degree of dysmenorrhea might also be looked upon as indicative of a condition of hypoövarianism. Such apparently contradictory conclusions may be reconciled in that the peculiar fat distribution occurred only after attainment of height maturity and the osseous development occurred as the result of factors for bone elongation, the force of which was sufficient to delay epiphyseal closure until a nearly normal chronological age.

Appendicitis, whether causative or coincident, in this case, must be considered seriously for the reason that removal of

this organ was followed by immediate relief from excruciating backaches, bearing-down pains, pains in the legs, uterine cramps, headache and somnolence which occurred either preceding, during or following the act of menstruation. Surgically, sufficient disturbance of the generative tract was not found to account for this series of symptoms. The uterus, tubes and ovaries were free from adhesions and inflammatory processes; however, the appendix did contain two fecoliths. The question naturally arises as to whether or not the marked degree of dysmenorrhea was the result of appendiceal disturbance or the result of gonadal disorder. It appears that had dysmenorrhea been the result of gonadal disturbances, the removal of the appendix would not have resulted in the immediate relief of these symptoms. However, the presence of a "colicy" appendix might have been sufficient to precipitate the array of disturbances at a time of general pelvic engorgement or during the menstrual period. Such an assumption would demand the presence of such an irritant from the very beginning of menstruation. Such an excitant might have had its origin in the severe attack of appendicitis and the sacral injury, both of which occurred preceding the establishment of menstruation. Whether or not these two accidents were instrumental in exciting precocious menstruation, of course, is impossible to say. Inasmuch as definite disorder of the ovaries was lacking, the relation between the appendiceal condition and the appearance of dysmenorrhagic menstruation becomes of more importance. Irrespective of such a possible relation it can be said that precocious menstruation and the establishment of sex characters associated with the somatic development was not the result of demonstrable tumor formations in the ovaries or suprarenals. Of course a tumorous condition may have been present; however, if present it left no signs by which it could be recognized by gross inspection at operation. We may conclude that this case is representation of those cases of early menstruation due to factors other than tumor masses in the ovaries.

CONCLUSIONS

1. A study of two cases of precocious menstruation is presented.

2. Consideration of these two cases fails to reveal any defi-

nite causative factor for the appearance of precocious menstruation.

3. Early menstruation, as evidenced by the second case presented, may occur independent of demonstrable gross pathology of the ovaries.

BIBLIOGRAPHY

Bell, W. B.: The sex complex. N. Y., 1916. Wm. Wood & Co., 233, pp. 8°.

Brohl: Ovarialkystome in 7-jähriges Mädchen, Zentralbl. f. Gynäk. (Leipz.), 1897, 21, 113.

Falta, W.: The ductless glandular diseases. Transl. & ed. by M. K. Meyers, Phila., 1915, P. Blakiston's Son & Co., 692 pp., 4°.

Harris, R. H.: Carcinomatous ovarian teratoma with premature puberty and precocious somatic development. Surg. Gynec. & Obst. (Chicago), 1917, 24, 604-611.

Klein: Ein Fall von Pubertas praecox. Deutsche med. Wchnschr. (Leipz. u. Berl.), 1899, 47.

Krabbe, K. H.: Early synostosis of the epiphyses with dwarfism in pubertas precox. This Journal, 1919, 3, 459-466.

Leiner, J. H.: Pubertas precox with especial attention to mentality. This Journal, 1920, 4, 369-380.

Lenz, J.: Vorseitige Menstruation, Geschlechtsreife und Entwicklung, etc. Arch. f. Gynæk. (Berl.), 1913, 99, 67-144.

Lespinasse, V. D.: The testicle as a gland of internal secretion. Endocrinology and Metabolism. D. Appleton & Co., N. Y., 1922, 2, 491-523.

Lucas, R. C.: Tumor in the right ovary in child aged seven years, associated with precocious puberty; ovariotomy; cure. Tr. Clin. Soc. Lond., 1888, 21, 224-227.

Neurath, H.: Die Vorzeitige Geschlechtsentwicklung (Menstruatio praecox). Wien. med. Wchnschr., 1909, 59, 1301-1313.

Novak, E.: Menstruation and its disorders. Gyn. & Obst. Monographs, N. Y., 1921, D. Appleton & Co., 357 pp., 8°.

Riedl, H.: Menstruation praecox und Ovarialsarkom. Wien. Klin. Wchnschr., 1904, 9, 942.

Wolff. B.: Zur Kenntniss der Entwicklungsanomalien bei Infantilismus und bei vorzeitiger Geschlechtsreife. Arch. f. Gynæk. (Berl.), 1911, 94, 542-579.

THYROID STUDIES I. THE DISTRIBUTION OF GOITRE AMONG INDIANS; ITS BEARING UPON THE ETIOLOGY

HOMER P. RUSH and L. T. JONES

From the Department of Physiology of the University of Oregon
Medical School

PORTLAND

"Goitre" is here used in its broad sense to indicate all thyroid enlargements. Even a meagre review of the literature will show the complexity of this condition by the numerous theories offered. The outstanding factors concerning the etiology which seem to have the most accurate scientific support are iodine deficiency [Marine and co-workers (1)] and the accumulation of toxic products [McCarrison (2) and others (3, 4, 5, 25)].

Marine and his co-workers have shown the great affinity of the thyroid for iodine (1). Many investigators have shown the constant presence of iodine in thyroid tissue. Iodine as such has been used with favorable results for treating goitre since the early part of the nineteenth century (1). In 1917, Marine, Kimball, Lenhart and Rogoff demonstrated the beneficial effect of iodine as a prophylactic in cases of thyroid instabilities. Since then this work has been repeated in Switzerland and also in this country (9). The results point strongly toward a relationship between thyroid disturbances and the iodine obtainable. An uneven distribution of iodine throughout the country suggests that goitre districts are probable iodine deficiency districts. The early works of Forbes and Beegle (6) on iodine distribution throughout the United States needs supplemental information because of later improved methods for iodine determination. McClendon (7, 8) has undertaken a recent study of iodine distribution by an improved technique. In this preliminary report he shows a striking parallelism between iodine distribution and goitre districts. These results are indicated in Figure II. The statistics for goitre incidence used by McClendon are those

compiled by the War Department and are the only ones available for the country at large.

Many investigators have shown the effect of various toxic materials upon the thyroid gland. McCarrison found that fecal contamination could produce thyroid changes (2). Burget produced changes in the histological appearance of the gland by unhygienic surroundings (3). Sows which are fed a high protein diet, thus increasing intestinal putrefaction, gave birth to goitrous pigs (11). Therefore not only the iodine assimilation but toxic materials as well have been shown to affect this gland.

It appeared to us that an approach toward the selection of fundamental factors involved might be made by a detailed study of the incidence and distribution of the disease. Such a study would indicate the location of goitrous regions. The factors peculiar to these regions could then be studied. Many limited survey studies have been made and goitre districts of this country as well as the world at large have been mapped out, yet it seems that no satisfactory explanation has been given which will apply equally to all of these districts. A complete survey of the incidence of goitre in this country would be invaluable. Such an undertaking is beset with numerous difficulties. We believe that a contribution might be made by undertaking a goitre survey of one class of people, inclusive enough to be indicative of the whole country yet small enough to make possible a careful survey. A class should be chosen which is made up of un-nomadic inhabitants of the localities being investigated. This class must be one that would not show any racial immunity to the disease.

The native North American Indians seem to meet all requirements very well. This race is numerous enough to give indicative figures of the localities being investigated. Moreover, the Indian population is not too massive for an accurate survey, especially since the tribes are cared for on reservations under supervision. A study of Indian life shows the un-nomadic characteristics of the race. This is probably more pronounced with the Indian than with any other class of American people (12). Consequently these people have not come under the influencing factors of outside regions. Since the Indians have

goitre and the incidence is very high in some districts, racial immunity does not exist.

Our information concerning the incidence of goitre among the Indians was kindly furnished by Doctor R. E. L. Newberne, Chief Medical Supervisor of the Indian Commission. A questionnaire was sent throughout the Indian population during the Fall and Winter of 1922-1923. The data were gathered by the respective Indian physicians, compiled by the Indian Commissioner's office and forwarded to us. The results obtained from this survey are shown in Figure I, the incidence of goitre being arranged according to States.

Figure I. Indian surveys. Goitre incidence by states. Lower and left hand half indicates incidence of goitre as shown by the survey of 1908 (Hrdlicka). The upper and right hand half indicates the incidence as shown by the survey of 1923. States left blank indicate states from which no statistics were obtainable.

A complete goitre survey among the Indians was compiled in 1908 by Hrdlicka (13), who was working, at that time, in conjunction with the Indian Commission. These data are shown in Table I; they give the proportions per thousand of population for the various tribes. We have rearranged these figures to show the incidence of goitre according to States.

A study of the results of these Indian surveys shows goitre to be present among this race. It also bears out the generally reported observation that goitre in the United States is regional

TABLE I

Goitre among Indians. Proportions per thousand of population.

Tribe	State	Per 1000	Tribe	State	Per 1000
Blackfeet and Sioux	S.Dak.	61.4	Shoshoni and		
Ute	Utah	35.4	Arapaho	Wyo.	3.6
Oneida	Wis.	26.7	Mission Indians	Calif.	3.1
Cheyenne	Mont.	25.6	Apache (White Mt.)	Ariz.	2.9
Sioux	S.Dak.	14.3	Sioux (branch)	S.Dak.	2.9
Menominee	Wis.	10.9	Sioux (branch)	S.Dak.	2.9
Indians (Genoa			Sioux (branch)	N.Dak.	2.8
School)	Nebr.	10.0	Hopi	Ariz.	2.1
Sioux (branch)	S.Dak.	7.8	Oneida	Wis.	1.9
Chippewa	Mich.	6.7	Cheyenne	Okla.	1.8
Crows	Mont.	6.6	Coeur d'Alenes	Wash.	1.7
Indians (Ft. Ber-			Piegan	Mont.	1.5
thold)	N.Dak.	6.6	Pawnee	Okla.	1.6
Southern Ute	Colo.	5.6	Yuma	Calif.	1.5
Rio Grande Pueblos	N.Mex.	5.3	Cherokee	N.Car.	1.4
Sioux (branch)	S.Dak.	4.3	Apache	S.Colo.	1.3
Sioux (branch)	Mont.	4.2	Sioux (branch)	S.Dak.	1.2
Navajo	Ariz.	4.1	Sioux (branch)	S.Dak.	1.1

From Bull. 34 Bur. Am. Ethnology. Physiological and Medical Observations among Indians. Hrdlicka.

in distribution. These regions are considered to be in the Pacific Northwest, the North Central States, Great Lake District and in the Appalachian Highlands. Thus, excepting the Pacific Northwest, the incidence among Indians is roughly parallel with the incidence among the population as a whole. It will also be further seen that goitre has been increasing among the Indians. This increase seems to be quite general although more pronounced in the goitre regions. The number of cases reported in 1908 was 376 for an Indian population of 125,000, giving an incidence of three per thousand. In 1923, this increased to 3092 cases for a population of 189,200, giving an incidence of 16.3 per thousand.

In the light of Marine's work to which reference has been made it would seem most logical to turn to a possible iodine deficiency as the etiological basis for this affliction. While definite experimental data are incomplete to show this factor to be responsible for goitre development, the prevention work with iodine is highly suggestive. If this deficiency is the cause, districts with a scarcity or absence of iodine must be present and these districts must coincide with the goitre districts. McClendon's work points in this direction but, as the author states, it is far from complete (7, 8).

Because of the lack, then, of complete information concerning iodine distribution, attention may be turned to these conditions that may influence its deposition. Iodine is found in small quantities on the earth's crust widely distributed, but by far in greatest amounts in the sea. It is the most sparingly deposited of the halogen salts (14). Analysis of sea-water shows iodine to always be present, the amount usually being stated as 100 mg. per litre. Iodine is found in nature almost exclusively as sodium iodide, the most soluble of natural salts. This salt is about five times as soluble as sodium chloride. This difference of solubility can easily account for the abundance of sodium chloride and the scarcity of sodium iodide.

When salts are deposited the most insoluble will be the first to reach saturation and consequently deposition (16). On the contrary, the most soluble will be the last deposited. Thus the most soluble salt will continuously be kept in solution if more water is added to the evaporating body of liquid and also it will be the soluble salt which will run off if the supernatant fluid escapes. Therefore, as Hayhurst has indicated (14), iodine is scarce upon the earth's crust because: (1) "it has been carried off by supernatant fluid during the process of the drying-up of saline waters; (2) the dissolving-out process that occurs as a result of the percolation of the rains and subterranean waters carries out the soluble salts (iodine); (3) the pent-up deposits and brines have been perfused so long by fresh waters as to carry away their more soluble constituents."

Geographic districts that would be favorable to iodine deficiency should therefore be those regions which show at least some of the following meteorological and geological characteristics. First, they must have been thoroughly washed by fresh water perfusion. This may have been caused by the washing from the melting of old glaciers, the percolation of abundant rainfall or the perfusion by subterranean waters. Secondly, the slope of the country must be such that the water will rapidly flow off, thus removing the soluble constituents from the region. Thirdly, these regions farthest removed from the sea would have the least opportunity for replenishing the iodine lost.

The goitre districts of this country are situated in such regions. The Pacific Northwest, although of relatively recent

geologic origin, has been, nevertheless, subjected to many washings. The flow from the old glaciers passed over this country. Again we find great fresh water perfusion as the result of heavy yearly precipitation. Notwithstanding that this country is along the sea coast, its slope is such as to favor rapid movement of both surface and subterranean waters. No other sea coast of the United States has the slope or the precipitation this coast shows. Therefore iodine loss might be expected to be greater than any iodine deposition from sea air. Consequently iodine deficiency can be expected.

The Rocky Mountain States are in a rugged country. Although their rainfall is but moderate, the slope offers rapid drainage. As has been indicated by Hayhurst (14), the mountains are the first to lose their supply of iodine. The glacier water also washed these soils. Therefore this district should also show an iodine deficiency.

The Great Lakes territory was influenced more by the glacier period than any of the vicinities previously mentioned. The precipitation of this district is moderate and the slope gentle. Consequently it would seem that past periods have had more bearing upon the depletion than present conditions. However, the continual fresh water perfusion that is now taking place makes the depletion more complete. On the other hand, the Appalachian Highlands are apparently affected more by percolating rains and fresh water perfusion. It may be pointed out that the area in western North Carolina shows the heaviest rainfall of the East. This district is also mountainous, which insures rapid drainage. Thus, if our hypothesis is correct, other iodine deficiency areas should be located in these regions.

The South appears to be comparatively free from goitre. This part of the country has a gentle slope. The waters which arise in the North, particularly the North Rocky Mountain, North Central and Great Lakes States, flow down over the gentle slope of the South. During the course of this flow the more soluble substances of the soil will be carried off from the North, only to be deposited in those regions where evaporation makes the concentration sufficient. As evaporation is continually taking place and as the Southern States have the gentle slope which retards the movement of the flow, iodide salts could be

deposited in these regions. Moreover, as the slope at the sea coast is much less abrupt in both the East and South, iodine deposited from the sea air should not be washed out as rapidly as in the Northwest. The Southwestern States are the most arid of the United States. Although this district is somewhat mountainous, the geographic formation is more of a high plateau. As a result of these conditions the percolation due to rainfall and the fresh water perfusion is lacking. The Southern States were not affected by the glacier period and consequently the South should be a land rich in iodine.

Previously it was stated that the results from the Indian survey (1923) indicated a parallelism of the incidence of goitre among the Indians and the country at large. Exceptions, however, will be noted as occurring in the Pacific Northwest. In this area goitre was practically absent from the Indians in 1908 and at the present time is much less frequent than among the white race. Three explanations may be offered for this variation. The primary cause, apparently, is found in the Indian diet. The American Indian, like most aborigines, uses those articles of food most easily obtained (12). Among the chief substances of diet of the Northwest Indians is salmon, and to a lesser degree other sea foods. Salmon composes a very large part of the diet not only during the fishing season, but it is eaten in the dried form a greater part of the year. Fishing is universal among these Indians and even the inland tribes obtain this sea food. Jordan (20) has shown that salmon run to the headwaters of the Northwest streams to a distance of 2500 miles. It has been shown [Cameron (21)] that "all sea species of animals contain iodine." The iodine obtained from the diet of salmon by the Indians should, on the basis of Marine's results, serve to prevent the development of goitre. Attention may also be called to the fact that the Indian of the North depended also in a large part on game for food. Unlike the white people, the Indians utilized the whole animal, which would include thyroid gland in the diet. The average amount of iodine found in thyroid tissues varies from 0.050 to 0.777 mg. per gm. of fresh tissues (1), depending upon the activity of the gland. Even so small an animal as the rabbit would furnish about 0.155 mg. of iodine. As it has been shown that 100 to 200 mg. of iodine twice

Figure II. Shows the incidence of goitre per thousand as determined in "Defects Found in Drafted Men, War Department, 1920," and the amount of iodine in the water. The curves have been rounded off. (McClendon, 7.)

Figure III. The shaded areas show the annual precipitation of the United States (U. S. Department of Agriculture. Weather Bureau, Bull. Q. Climatology of the United States, by A. J. Henry). The dotted line indicates the old glacier line·from which waters flowed over the northern part of the United States. (Geology by Chamberlain and Salisbury.)

a year is sufficient to prevent simple goitre in man (1), this source of supply would offer a significant amount. Third, it may be suggested that the modern method of agriculture tends to rob the land of iodine without any means of replenishing the supply. This is brought about by the constant use of the soil, the plants taking up the available iodine. The greater ease of fresh water perfusion in cultivated land is also a factor. Studies made in Germany (22) show an increased amount of goitre during the war, which is in part explained as due to the discontinuation of nitrates, containing also iodides, shipped in from Chile and the substitution of guano for fertilization.

This survey shows a decided increase in incidence of goitre among the Indians. It would seem that the tendency of the Indian to adopt the habits of civilized life can not account for it. If this were the case, the whites of non-goitrous regions should show a higher incidence. The diet, however, deserves consideration. In the Northwest, for instance, the salmon is taking a smaller and smaller place in the diet of the aborigines. This scarcity of salmon for the Indians has already been the cause of much complaint and court action (23). The purified foods, including white salt, are becoming the larger part of the diet. Thus the Indian of this district is being placed under the same living conditions as the whites. He also is starting to show the same high incidence of goitre as found among the white people of this district. In other parts of the country the sea food factor is eliminated. However, the question of diet is not eliminated. The Indian of today has not the quantity of wild game which was previously consumed. The salt supply of these natives was often crude salt which in many localities contains iodides. It would seem, then, that the purified diet may be a factor concerning the increased incidence of goitre in other districts.

Two districts other than the Northwest show decided increases of goitre that deserve special note. Oklahoma shows an increase from .02 per thousand to 1.6 per thousand. This State has been the great gathering point for many Eastern tribes. Although a careful study of the conditions could not be made, it seems probable that a change in environmental factors would explain this increase. North Carolina has an incidence which

has increased about 8000 times during the interval between surveys. These conditions, likewise, could not be carefully studied. The entire results from the second survey were obtained from the Cherokee school situated at Ashford, North Carolina. This city is also in the heart of the East's greatest precipitation area as well as being in a mountainous country. Therefore the factors are present in this locality which would favor iodine depletion.

Utah, although partly in the arid region, shows a high incidence of goitre in both surveys. This State's average is accounted for by the high incidence found among the tribes located in the northeastern part of the State. This location has a moderate rainfall and also is a more mountainous district than the rest of the State. The tribes of southern Utah show practically no goitre.

While most of our evidence points to iodine deficiency, the second class of etiological agents, i. e., toxic products, seems to play its part. Investigations have indicated that changes occur in the thyroid tissue following the administration of fecal substances (26). Such data would suggest an increased demand made upon the thyroid during intoxications by such substances. Farrant (25) has shown that many intoxicating diseases cause an increased activity of the thyroid gland as demonstrated by hyperplasia of this gland. He has even classified diseases by the manner in which they affect the thyroid substance. Among the afflictions which cause this change in the gland is tuberculosis. The increasing prevalence of this latter disease among the Indians has long been shown (24). It is suggested that the body needs more iodine during such a strain upon the organism and leads to the assumption of an iodine balance in this gland. As McCarrison (19) has pointed out, an iodine sufficiency may become a deficiency if some extra load is thrown upon the gland.

SUMMARY

1. Goitre is present among the Indians and the incidence of distribution is, for the most part, parallel to the distribution among the white population.

2. The greatest exception is noticed in the Pacific Northwest, where the natural Indian diet contains more iodine (salmon) than does the white man's diet.

3. Goitre is increasing among the Indians and this increase seems to be explainable by two factors, iodine deficiency and toxic influences upon the organism.

4. Simple goitre seems to be the result of iodine deficiency, produced by a low amount of iodine or an increased thyroid demand.

5. These results seem to offer further support of the work by Marine and co-workers (1) and McClendon (7).

BIBLIOGRAPHY

1. Marine, D., Lenhart, C. H., Kimball, O. P., Rogoff, J. M.: Compiled by G. N. Stewart. Western Reserve Univ. Pub., May 7, 1923.
2. McCarrison: The thyroid gland in health and disease. Wm. Wood & Co., N. Y., 1917.
3. Burget, C. E.: Am. J. Physiol. (Balt.), 1917, 44, 492.
4. Watson, C.: J. Physiol. (Lond.), 1906, 34, 111.
5. Bensley, R. R.: Anat. Record (Phila.), 1914, 8, 431.
6. Forbes & Beegle: Bull. 299 Ohio Agr. Exper. Sta., 1916.
7. McClendon, J. F.: J. Am. M. Ass. (Chicago), 1923, 80, 600.
8. McClendon, J. F.: Science (N. Y.), 1922, 56, 269.
9. Kimball, O. P.: U. S. P. H. R., 1923, 38, 877.
10. U. S. War Dept.: Defects found in drafted men. 1920.
11. Hart & Steinach: J. Biol. Chem. (Balt.), 1917, 3, 313.
12. Bull. 30 Bur. Am. Ethnology. Handbook Am. Indians.
13. Hrdlicka: Bull. 34, 1908, Bur. Am. Ethnology.
14. Hayhurst, E. R.: J. Am. M. Ass. (Chicago), 1922, 78, 18.
15. Blackmore: Chem. Abst. (Easton), 1912, 6, 2055.
16. Phalen, W. C.: Bull. 669 U. S. Geological Survey Salt Resources of U. S.
17. Chamberlain & Salisbury: College textbook of geology. Henry Holt & Co., N. Y., 1909.
18. U. S. Dept. Agr., Weather Bureau, Henry, A. J.: Bull. Q, Climatology of the U. S. 1906.
19. McCarrison: J. Am. M. Ass. (Chicago), 1923, 81, 1725.
20. Jordon, D. S.: Fishes. Henry Holt & Co., N. Y., 1907, 299-300.
21. Cameron: J. Biol. Chem. (Balt.), 1914, 18, 335. Ibid., 1915, 23, 1.
22. Bleyer: München. med. Wchnschr., 1922, 69, 587-589; this Journal, 1922, 6, 726.
23. Communication from Indian Service.
24. Report of Committee of Nat. Tuberc. Ass., appointed Oct. 28, 1921, on tuberculosis among the North American Indians. U. S. Indian Affairs Office. General Pub., 1923.
25. Farrant: Lancet (Lond.), 1913, 11, 1820. Brit. M. J. (Lond.), 1914, 1, 470.
26. Rush & Jones: Unpublished work. Univ. Ore. Dept. of Physiology.

A CASE OF TETANIA PARATHYREOPRIVA TREATED WITH COLLIP'S PARATHYROID EXTRACT[*]

By H. LISSER, M.D., AND H. C. SHEPARDSON, M.D.

SAN FRANCISCO

It is unnecessary for the purposes of this brief paper to sketch the historical aspects of our knowledge regarding the pathogenesis of tetany. That tetany invariably follows removal of the parathyroid glands has been abundantly confirmed. Furthermore, many years have elapsed since MacCallum and Voegtlin demonstrated a low blood calcium content during attacks of tetany and showed that such attacks could be controlled or ameliorated by the intravenous injection of calcium. Inasmuch as severe parathyroid deficiency causes tetany, and since a striking diminution in the calcium content of the blood is always found under such circumstances, it seems altogether likely that calcium metabolism is, to some extent at least, regulated by parathyroid function.

Attempts to substitute for lack of parathyroid hormone in cases of tetania parathyreopriva, by administration of variously prepared parathyroid extracts, have been unsuccessful, the explanation for failure being the logical assumption that the preparations were inert and did not contain an active parathyroid hormone.

Late in 1924, J. B. Collip, Professor of Biochemistry at the University of Alberta, Canada, announced "the extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium." Thus another hormone of unquestionable potency was added to the list of thyroxin, insulin, pituitrin and adrenalin. Space forbids an adequate review of the elaborate and painstaking experiments on normal and parathyroidectomized dogs to whom this extract was administered; and the reader is referred to the articles by Collip and coworkers (1, 2, 4) which have appeared in The Journal of Biological Chemistry (1925). Suffice it to state

---

*From the Department of Medicine, University of California Medical School, San Francisco, California.

383

that a stable and purified extract was prepared which, when injected subcutaneously, produced a rise in the blood calcium level, and which in overdosage produced an alarming and usually fatal hypercalcemia. It was furthermore shown that frequently repeated small doses of this extract are cumulative in action and will eventually raise the blood calcium to dangerous levels (values over 15 mg.), due to a "pyramiding of the effect of each successive injection upon the preceding one." Hence the importance of accurate and dependable blood calcium determinations to control the dosage, very much as one checks the administration of insulin by blood sugar estimations, and watches the effect of thyroid extract by determinations of the basal metabolic rate.

Eli Lilly and Company, in collaboration with Professor Collip, have prepared this parathyroid extract for clinical use.* The extract is standardized by its capacity to increase the total blood-serum calcium in normal dogs; and one unit is defined as one-hundredth the amount of extract required to cause an increase of 5 mg. of calcium in the blood-serum of a 20 kilogram dog, the rise of calcium being determined fifteen hours following the injection of the extract.

Tetania parathyreopriva is a comparatively rare experience nowadays since surgeons have learned to avoid the parathyroid glands in subtotal thyroidectomies. The complication may, nevertheless, occur even in the hands of skillful and experienced goiter surgeons, especially in the removal of large goiters adherent to the trachea and with substernal extension. It so happened that the appearance of symptoms of tetany in a patient, following thyroidectomy, provided us with the opportunity of administering Collip's parathyroid extract, to which the surgeon kindly consented, and which we were able to control accurately by repeated blood calcium determination. The laboratory, under the direction of Dr. Langstroth, used the Collip modification of the Kramer-Tisdall method (3) for estimation of blood serum calcium. Every precaution was used in the preparation of the syringes, needles, test tubes and apparatus to eliminate errors from calcium present in tap water. Many

of the specimens were checked in two different laboratories to insure accuracy.

We are aware of the fact that others in the United States and elsewhere have had an opportunity of trying this extract but we have as yet found only three reports of its clinical use.

Collip and Leitch (5) (January, 1925) report the first case of tetany to receive treatment with parathyrin. A girl 22 months of age, who weighed only 15 pounds and 12 ounces and suffered from a pronounced case of rickets, became feverish suddenly, vomited, breathed very rapidly (60 to the minute) and showed marked carpopedal spasm, hyperactive reflexes, and Chvostek's phenomenon. During the first two days, three doses of 1 cc. of Collip's parathyroid extract were given hypodermically. Improvement was so prompt and satisfactory that for the following four days 1 cc. of the extract was given by mouth twice daily, and finally for ten days 1 cc. by mouth daily. At the time of writing, one week had elapsed since the last dose of extract and no further evidence of tetany had developed.

In the course of an article on "Surgery of the Glands of Internal Secretion," Crile (6) writes as follows: "During the past six weeks we have been using the hormone discovered by Dr. J. B. Collip of Alberta University and have secured as definite results as he secured with his experimental animals in both acute and chronic cases of tetany. Five acute cases have been treated with relief in every case. Relief of symptoms is usually experienced within twenty minutes to one-half hour after the intravenous injection of 1 cc. of the hormone. In one exceedingly acute case, in which not a single one of the classical symptoms of tetany was lacking, the first dose was followed within twenty minutes by a disappearance of the subjective symptoms. Three doses of 2 cc. each resulted in complete recovery. Among the chronic cases treated, relief has been secured in about 85 to 90 per cent."

Davidson (7) (August, 1925) reports "a case of adolescent myxedema, accompanied by nephrosis and by tetany of parathyroid origin, treated with thyroid and Collip's parathyroid extract." A girl, aged 17 years, developed in December, 1922, a marked edema, followed by convulsions, there being some remission in summer of 1924, and marked recurrence in November,

Blood calcium was low. Under thyroid and calcium chloride the symptoms of myxedema almost disappeared and convulsions markedly diminished in number and severity. Commencing January 28, 1925, thyroid 6 grains daily, was continued, the calcium chloride discontinued, and daily injections of Collip's parathyroid extract begun, the dose being adjusted until the blood serum calcium remained constant between 10.9 and 11.5 mg. per 100 cc. The necessary dose for this was found to be at this period 2 to 4 cc. of the extract per day. On this treatment edema completely disappeared and the convulsions were controlled almost completely. This treatment was continued for two months, during which time the situation was complicated by influenza, otitis media, rubella and diphtheria. On April 1st she left the hospital and returned to her home in the country, and was without therapy for several weeks, but relapsed and on May 19th, on return to the hospital, was in a more critical condition than ever, but by the same treatment was restored to apparent normality within 14 days of readmission to the hospital. However, further infections developed and the .patient finally died July 17th of severe toxemia of undetermined origin. Post-mortem examination revealed a very small atrophic thyroid gland and no parathyroids in either upper or lower normal positions; two were found in median positions, the left one somewhat atrophied and the right apparently normal. A chart includes percentage of albumen in the urine, several blood cholesterol and blood urea and basal metabolism determinations, and a great many blood serum calcium determinations together with the daily dose of parathyroid extract.

THE AUTHOR'S CASE

The patient, an obese woman 30 years of age, first visited the University of California Out-Patient Department in March, 1925, complaining of a goiter accompanied by mild dizziness, palpitation and nervousness. Her family history is unimportant, her father, mother and three sisters all being alive and well. She has been rather unfortunate in her marriages, her first husband having been a drug addict from whom she was divorced, without having been pregnant, four years after her marriage. Her second husband now has tuberculosis. There

are, however, three children living and well and she has had no other pregnancies. Libido is normal.

Her past history is interesting in that she lived only the first three years of her life in the northern part of California, a locality that is definitely a "goiter district." During the remaining twenty-seven years she has lived in or near San Francisco. She has been quite well educated and has been comparatively free from illnesses except for several attacks of tonsillitis which finally necessitated tonsillectomy when she was about 20 years of age.

She began menstruating at the age of 14 and her periods have been more or less irregular, the intermenstrual period varying from 14 to 40 days, averaging, however, approximately 28 days. The periods extend over from 1 to 3 days and are somewhat scant.

Soon after the onset of her menstrual function, she began to gain in weight. At the age of 15 her weight was about 130 pounds and she maintained this until her first child was born, at the age of 22. At that time the physician who attended her called her attention to the presence of a goiter. Following her delivery, she gained 70 pounds in one year (that is from 130 to 200 pounds). She weighed at the time of her first visit 225 pounds.

While she was somewhat vague about the onset of her symptoms (dizziness, nervousness and palpitation), she stated that they probably appeared sometime before the presence of the goiter, which was called to her attention at the age of 22. Their etiology is probably largely psychic, resulting from her unfortunate marriage to a narcotic addict at the early age of 15. As a matter of fact, when she separated from her husband some four years later, she had a mental upset which necessitated her remaining in bed for some six months, during most of which time she was irrational.

An interesting commentary on her disturbed metabolism is the fact that with each of her three pregnancies two teeth decayed completely.

Except for her marked adiposity, which had a tendency to be confined more or less to a girdle distribution, her physical examination disclosed no definite abnormalities except those

referable to her goiter, and there was but little evidence of toxicity. Her skin was somewhat moist; she had a slight tremor of the extended fingers and a blood pressure of 150/80. There were numerous large, soft, semifluctuant nodules easily palpable in the region of the thyroid gland. Her basal metabolic rate was 40.8% above the theoretical normal, but she did not co-operate well during the test.

Blood count was normal, as was the urine examination, except for the slightest possible trace of albumin in the voided specimen. Wassermann was negative. Roentgenological examination of the chest revealed a small substernal extension of the thyroid, causing some compression of the trachea.

In view of the fact that her goiter had recently been increasing in size and that there was evidence of beginning toxicity, surgical removal was advised, but the patient was unable to enter the hospital until several months later. On September 24, 1925, subtotal thyroidectomy was done under gas and oxygen anesthesia. The gland was found to be approximately ten times its normal size, extending posteriorly behind the trachea on both sides and with bilateral substernal extension. It was quite nodular and many small to medium sized adenomata could be palpated throughout the gland substance. These were removed and at the close of the dissection, minute portions of thyroid tissue remained over the trachea and in the region of the isthmus. The wound was closed without drainage and patient was returned to the ward in excellent condition.

On the evening of the second day, post-operative (September 26th), patient first noticed that the right thumb was drawn across the palm in spasm. From this time on she felt progressively more nervous and noticed muscle twitchings in various parts of her body, which gave her the sensation of ''innumerable tiny quivering foci'' in the muscles. Particularly did she notice almost a constant spasm of the muscles of the hands and feet. Two days later, these symptoms having constantly increased in severity and tetany being suspected, the writers were called in consultation.

Examination revealed a very apprehensive individual, nervous, frightened and in considerable pain from the various muscle spasms, especially of her hands and feet. Positive Chvostek

and Trousseau signs were easily elicited, Erb's phenomenon was markedly positive, the anodal opening contraction occurring with 3 milliamperes, the cathodal and anodal closing contraction occurring with 4 milliamperes when the right ulnar nerve was stimulated with galvanic current. In fact, she presented a classical picture of a· moderately severe parathyroid insufficiency.

She had been given one gram of calcium lactate by mouth prior to this examination, and at 4 p. m. September 28th her blood serum calcium was 8.1 mg. per 100 cc. of blood. Treatment for the next three weeks was restricted to injections of a parathyroid extract, no calcium being administered and no modifications of the diet instituted. She was given 12½ units of parathyroid extract intramuscularly, but the following morning her fasting blood serum calcium was 7.6 mg. per 100 cc. of blood. On September 29th she received 25 units of parathyroid extract and subjectively felt much improved in spite of the fact that the fasting blood serum calcium on September 30th reached a low level of 7.2 mg. per 100 cc. The dosage of parathyroid extract was increased to 37.5 units on September 30th. On that day the Chvostek and Trousseau signs were still obtainable but much less marked than on the previous day and the patient stated that she "slept better the preceding night than she has for years." However, she did have some cramps in her feet during the night as well as occasional spasms of the epigastric muscles. On October 1st her fasting blood serum calcium had risen to 8.4 mg. per 100 cc.

Fluid had gradually collected in the wound and on October 1st, 35 cc. of serum were aspirated. On October 1st and 2nd, 37½ units of parathyroid extract were administered daily. The blood serum calcium remained at 8.4 mg. per 100 cc. but the patient improved subjectively. She had no more parasthesias, was no longer nervous or "jumpy" and during the night had only one leg cramp. Chvostek and Trousseau signs remained slightly positive. On October 3rd her fasting blood serum calcium was 8.7 mg. per 100 cc. and the parathyroid extract was reduced to 25 units daily. Her fasting blood serum calcium continued to rise, showing a cumulative action of the parathyroid extract, until on October 5th it reached 9.7 mg.

per 100 cc. The dosage of parathyroid extract was further reduced to 12½ units on October 5th and discontinued entirely October 6th. She was then completely free of symptoms, and Chvostek and Trousseau signs were not obtainable.

Coincidental with the discontinuing of the parathyroid extract, her fasting blood serum calcium began to drop. On October 6th it was 9.3 mg. per 100 cc. and on the 7th, 8.2 mg. per 100 cc. On the latter date the cathodal closing contraction occurred with 2.5 milliamperes while the cathodal opening contraction occurred with 3.5 milliamperes. Chvostek's sign was mildly positive and the patient complained of some superficial parasthesias over the forearms and a tendency for contractures of the middle, ring and little fingers. Her basal metabolic rate on this date was 13.8% above the theoretical normal, but she again failed to co-operate well. She was given 12½ units of parathyroid extract on October 7th and her blood serum calcium promptly rose to 10.7 mg. per 100 cc.

On October 8th, 35 cc. of serum was again aspirated from the wound and *no parathyroid extract was given.* Her fasting blood serum calcium immediately began to drop and continued to do so in spite of the administration of 5 units of parathyroid extract on October 10th and again on October 12th, reaching a low level of 7.4 mg. per 100 cc. on October 13th. Her general condition was good, no apprehension or other symptoms were present, but Chvostek and Trousseau signs were markedly positive. For some unexplained reason the electrical reactions obtained on October 13th were practically normal, the cathodal closing contraction occurring with 3.5 milliamperes and the cathodal opening contraction occurring with 7.0 milliamperes.

On October 13th she was given 25 units of parathyroid extract. The following day 10 units were given and on October 15th 10 units more were given. On October 16th Chvostek and Trousseau's signs could not be elicited and patient felt perfectly normal. The cathodal closing contraction occurred with 6 milliamperes and the cathodal opening contraction with 7 milliamperes. The fasting blood serum calcium, however, was still low—8.1 mg. per 100 cc. Because of the low blood serum calcium, 25 units of parathyroid extract were administered on October 16th, 17th and 18th. Her blood serum calcium on

October 19th rose only slightly to 8.2 mg. per 100 cc. As a result of this continued low fasting blood serum calcium, 50 units were administered on October 19th, 25 units being given about noon and 25 units about 9 p. m. On October 20th patient complained of listlessness, lack of energy, and preferred to remain in bed. Her fasting blood serum calcium was taken at 9 a. m. and found to be 10.5 mg. per 100 cc. The administration of extract was therefore discontinued and on October 21st the fasting blood serum calcium had risen even higher, it being 11.9 mg. per 100 cc.

After reaching this high level, the calcium content of the blood serum began to drop. On October 23rd it reached 8.4 mg. per 100 cc. Calcium lactate by mouth was then given, no parathyroid extract being administered. On October 23rd, 24th and 25th patient received 3 grams daily. The morning of October 26th her fasting blood serum calcium had again reached the low mark of 7.2 mg. per 100 cc. On October 26th the calcium lactate was increased to 8 grams and on October 27th she received 12 grams. However, the following day her fasting blood serum calcium was only 8.4 mg. per 100 cc.

It became evident that it would probably be impossible to force her blood serum calcium to normal by means of the oral administration of calcium lactate alone, and in view of the fact that the patient was again having symptoms, such as cramps in her feet and arms together with some parasthesias, her calcium lactate was, on October 29th, reduced to 5 grams daily and she was given 10 units of parathyroid extract every other day and kept on a general diet.

She was discharged from the hospital on October 30th because of the necessity of her returning to her family. She was carefully instructed in the hypodermic administration of the parathyroid extract, of which she will give herself 10 units every other day. In addition, she will continue to take calcium lactate by mouth, 5 grams daily in divided doses. Her fasting blood serum calcium on November 2nd was 8.9 mg. per 100 cc. and it will be checked once a week and oftener if necessity requires.*

---

*Blood serum calcium Nov. 6 was 8.8 mg per 100 cc. Beginning Nov. 9, she will give herself injections of 10 units of parathyroid extract daily instead of every other day. She is free from symptoms

Fig. 1. Chart of treatment administered, blood serum calcium response and reflex reactions.

·' The accompanying chart summarizes the above description,; and illustrates the response of the· fasting blood serum calcium· to injections of Collip's parathyroid extract. The status · of· nervous excitability is also recorded by the presence or absence of Chvostek's and Trousseau's phenomena.

. For the first few .weeks following operation there was some question as to whether the tetany arose from interference with the· blood supply of the parathyroid glands, or was due to their accidental removal. This doubt was finally settled when care-

Fig. 2. Section of parathyroid tissue found in removed specimen

ful search of all the tissue removed disclosed the presence of three separate parathyroid glands. This conclusively estab-lished the diagnosis of tetania parathyreopriva.

Gross ·Pathology: Specimen is two masses of tissue meas-uring 11x6x4 cm., weighing 235 grams. The anterior surfaces are encapsulated and nodular and the posterior show the rough

plane of resection. Cut surface shows multiple nodules, the largest 3.5 cm. in diameter, and their contents are degenerating colloid.

Multiple large and small degenerating adenoma of adult pattern in a thyroid gland.

Microscopic Pathology: Section shows closely packed adenomata. Small pieces of compressed gland proper are made up of small regular acini lined with flat epithelium and filled with dark staining colloid. The adenoma contents are large irregular acini, lined with flat to cuboidal epithelium and filled with dark staining colloid. Three separate parathyroids have been discovered. They were only found after very painstaking search and the sectioning of many blocks of tissue.

Diagnosis: Multiple large and small degenerating adenomata of adult pattern in a normal thyroid gland. Three normal parathyroid glands.

DISCUSSION

The case reported above is the first detailed record of tetany in a human being resulting from accidental parathyroid extirpation, in which Collip's parathyroid extract was used. We therefore had no previous experience from the literature to guide us in judging the dosage to be employed. It will be remembered that in Collip's original article he called attention to the fatal hypercalcemia which could be produced in dogs by injections of his extract. We therefore preferred to err on the side of conservative dosage, controlling the same by frequent determinations of the blood serum calcium. Collip's later experiments in which he contrasted the relative safety of single massive doses with the danger of frequently repeated small doses, had not come to our notice. In reporting these he stated that a long maintained hypercalcemia was invariably fatal while a sudden brief hypercalcemia was comparatively harmless. With this in mind it is interesting to observe that the two high peaks of blood serum calcium reached on October 8th and 21st, resulted from the cumulative effect of injections administered daily over a period of several days. Fearing a further rise of the blood serum calcium to dangerous levels, the administration of the extract was immediately discontinued on both occasions. That the effect of the dosages we employed was transitory is

shown by the fact that in each case five days later the blood serum calcium had dropped to the original low level of 7.2 mg. to 7.4 mg. per 100 cc. It is also interesting to observe that when the parathyroid extract was discontinued the second time, the blood serum calcium continued to fall despite the oral administration of ordinary doses of calcium lactate and was only slightly elevated later by fairly large doses.

Before we were certain that parathyroid tissue had actually been removed and while there was a reasonable possibility of the tetany being due to pressure ischemia from the collection of fluid in the wound, it was thought that possibly the first rise in blood serum calcium might be due to the aspiration of 35 cc. of serum rather than to the parathyroid extract injected. This assumption was shown to be false when a second aspiration of a similar amount of fluid eight days later at a time when parathyroid extract was withheld was accompanied by a fall rather than a rise of the blood serum calcium.

In our observation of this case, we were struck by the fact that subjective improvement was almost immediately effected by the parathyroid extract, and preceded by several days the objective improvement as evidenced by the reaction to Chvostek's and Trousseau's maneuvers, and that relief of symptoms occurred considerably in advance of any marked elevation of the blood serum calcium.

Collip states that the first definite symptom of parathyroid hormone overdosage observed in dogs was vomiting. We never pushed the blood serum calcium high enough in this patient to produce this symptom, but it is perhaps worth recording that when the blood serum calcium reached 11.9 mg. per 100 cc. she complained of listlessness and lack of energy and preferred to remain in bed, which was in sharp contrast to her feeling of well being on the previous few days.

It is perhaps premature at this writing to forecast the future of this patient, but it would seem likely that she can be kept free from symptoms and her blood serum calcium maintained at a normal level by the injection of small doses of parathyroid extract combined with calcium lactate by mouth.

In view of the fact that at least three parathyroid glands were inadvertently removed, it is altogether probable that treat-

ment will have to be continued more or less indefinitely. This is in accordance with the necessity for life-long administration of thyroid extract in pronounced myxedema. If this individual still possesses one parathyroid gland, compensatory hypertrophy may gradually ensue and eventually produce sufficient hormone to maintain a normal blood serum calcium. The authors hope to keep in touch with this patient and render a further report after long continued observation.

SUMMARY

1. A woman, 30 years old, was operated upon for a large adenomatous goiter. The mass extended under the sternum and posteriorly behind the trachea.

2. Three parathyroid glands were accidentally removed. The status of the fourth parathyroid gland is unknown.

3. The patient promptly developed tetania parathyreopriva.

4. A detailed account of the treatment with Collip's parathyroid extract together with its effect on the blood serum calcium is given in the text and summarized in a chart.

5. No calcium was administered during the first three weeks except for one gram of calcium lactate by mouth prior to beginning of parathyroid injections, and the patient was kept on a regular ward diet.

6. The effect of the parathyroid extract on the subjective symptoms, objective findings and blood serum calcium, is discussed.

7. This new parathyroid hormone seems to be a true specific for parathyroid tetany.

BIBLIOGRAPHY

1. Collip, J. B.: The extraction of a parathyroid hormone which will prevent or control parathyroid tetany and which regulates the level of blood calcium. Jr. Biol. Chem., 1925, 63, 395-438.
2. Collip, J. B., Clark, E. P., and Scott, J. W.: The effect of a parathyroid hormone on normal animals. Jr. Biol. Chem., 1925, 63, 439-460
3. Clark, E. P., and Collip, J. B.: A study of the Tisdall method for the determination of blood serum calcium with a suggested modification. Jr. Biol. Chem., 1925, 63, 461-464.
4. Collip, J. B., and Clark, E. P.: Further studies on the physiological action of a parathyroid hormone. Jr. Biol. Chem., 1925, 64, 485-507.
5. Collip, J. B., and Leitch, D. B.: A case of tetany treated with parathyrin. Canad. M. A. J., 1925, 15, 59-60.
6. Crile, G. W.: Surgery of the glands of internal secretion. Endocrinology, 1925, 9, 301-309.
7. Davidson, J. R.: A case of adolescent myxoedema, accompanied by nephrosis and by tetany of parathyroid origin, treated with thyroid and Collip's parathyroid extract. Canad. M. A. J., 1925, 15, 803-808.

HYPOPITUITARISM AND DIABETES

HENRY J. JOHN, M.D.

Cleveland Clinic

CLEVELAND

Anatomically the hypophysis cerebri is divided into three portions, the pars anterior, the pars intermedia and the pars posterior. Clinically, however, the pars intermedia and the pars posterior can not well be separated, as the extract of the pars posterior also contains that of the pars intermedia. The hormone of the pars anterior affects chiefly the osseous and the genital systems, hypersecretion producing gigantism early in life and acromegaly after growth has ceased, with secondary effects on the dermal system, temperature, pulse, blood pressure and mental function. The hormone of the pars posterior chiefly affects metabolism; hyposecretion produces increased carbohydrate tolerance and adiposity; hypersecretion, decreased carbohydrate tolerance with polyuria; it also causes contraction of the unstriped muscle.

I am interested chiefly in the relation of carbohydrate metabolism to variations in pituitary activity and therefore shall deal merely with this phase of the subject.

Engelbach (1) found that hyposecretion of the posterior lobe produced increased carbohydrate tolerance in 91.4 per cent of his cases and a decrease in 8.6 per cent. This is the general conclusion of most authors. But Engelbach found also that hyposecretion of the anterior lobe produced increased carbohydrate tolerance in 71.5 per cent of his cases and a decreased tolerance in 28.5 per cent. (See Table I.) It would appear therefore that the carbohydrate tolerance does not provide a definite criterion whereby to differentiate the functional ability of either of these two lobes of the pituitary gland.

Sachs and Macdonald (2) have found that in animals after the removal of the pituitary gland the fasting blood sugar was slightly lowered and a transient glycosuria which they consider of no importance followed the operation. When they removed

TABLE I

Glucose Tolerance in Pituitary Disease
(after Engelbach)

	Hypopitu-itarism Ant. Lobe	Hypopitu-itarism Post. Lobe	Hyperpitu-itarism Ant. Lobe	Hyperpitu-itarism Post. Lobe
Tolerance increased in.....	71.5%	91.4%	66.6%	66.6%
Tolerance decreased in.....	28.5%	8.6%	33.3%	33.3%

Anterior lobe dyscrasia, 10 cases—
　　Decreased carbohydrate tolerance in 7 or 70 per cent.
　　Increased carbohydrate tolerance in 3 or 30 per cent.
Hypopituitarism (anterior lobe), 7 cases—
　　Decreased carbohydrate tolerance in 2 or 28.5 per cent.
　　Increased carbohydrate tolerance in 5 or 71.5 per cent.
Hyperpituitarism (anterior lobe), 3 cases—
　　Decreased carbohydrate tolerance in 1 or 33.3 per cent.
　　Increased carbohydrate tolerance in 2 or 66.6 per cent.
Hyperpituitarism (posterior lobe)—3 cases—
　　Decreased carbohydrate tolerance in 1 or 33.3 per cent.
　　Increased carbohydrate tolerance in 2 or 66.6 per cent.
Hypopituitarism (posterior lobe), 58 cases—
　　Decreased carbohydrate tolerance in 5 or 8.6 per cent.
　　Increased carbohydrate tolerance in 53 or 91.4 per cent.

merely the anterior lobe the blood sugar was normal. They were unable to produce a permanent glycosuria experimentally. In all of these animals except those in which only the anterior lobe has been removed, the highest rise in the blood sugar curve was at the end of one hour, which suggests a lessened tolerance in contrast to the curve in normal animals in which the highest rise occurs at the end of one-half hour.

The data that I have been able to gather from the records of the Cleveland Clinic are as follows:

Total number of cases of pituitary disease—41.
Hypopituitarism, 31—
　　Without glycosuria, 26 or 83.8 per cent.
　　With decreased carbohydrate tolerance, including diabetes, 5 or 16 per cent.
Acromegaly, 7—
　　Without glycosuria, 4 or 57.1 per cent.
　　With glycosuria, 3 or 42.8 per cent.
　　With diabetes, 2 or 28.8 per cent.

As has been stated above, hypopituitarism suggests increased carbohydrate tolerance. That this rule does not hold invariably, however, is shown by Chart I, which shows the glucose tolerance curves secured in three cases of hypopituitarism, each of

which had the typical clinical symptoms of the disorder. The first (upper curve) of these patients was a man 51 years of age with typical voice changes, impotence for 5 years and lack of mental alertness. The x-ray plate showed the sella to be normal. The second case (middle curve) was a boy 22 years of age, who

CHART I

Glucose tolerance in cases of hypopituitarism

looked like a lad of 12 or 14 years. He had a high-pitched voice, undeveloped genitalia and was mentally dull. The x-ray plate of the sella showed no enlargement. The basal metabolism was minus 17.7 per cent. The third case (lower curve) was a man 36 years of age with diminished energy. He had lost most of the hair from all parts of the body, and was quite nervous; the genitalia were normal. Two of these patients showed a slight postprandial glycosuria, the renal threshold for sugar being apparently quite low in both. There was no glycosuria in the third case. The upper and lower curves are of the type which denotes increased carbohydrate tolerance. On the other hand, the second curve is a type which we get in normal individuals, and yet this patient had the most typical case of hypopituitarism in this group, showing all the signs of pituitary dysfunction.

Moreover, that an individual with hypopituitarism is not free from the disorder that is the most typical of a decreased carbohydrate tolerance, viz., diabetes, can be seen by the following cases.

Case I. A married woman 27 years of age. She had had no illnesses excepting tonsillitis and influenza. When I first saw her the menses were regular but scanty, but they ceased shortly afterwards (14 months ago); and adiposity has developed during the past few months, her weight rising from 125 to 205 pounds. There has been no disturbance in vision. She drinks and urinates excessively. Physical examination disclosed nothing of importance except an infantile uterus. The x-ray plate of the sella turcica shows a normal size and contour. There has been no glycosuria. The blood Wasserman test was negative. Blood urea was 24 mg. per 100 cc.; blood creatinin, 1.05 mg. The findings in the glucose tolerance test as shown on Chart II, upper curve, gave a typically diabetic curve with a fairly high renal permeability.

Case II. An unmarried girl, 18 years of age. In childhood she had had measles, mumps and chickenpox; later in life influenza, tonsillitis and rheumatism. Her tonsils and adenoids had been removed a year before. She complained of nervousness and stomach trouble. During the five months before I saw her she had gained 25 pounds in weight. Her hands were cold and she had marked perspiration. Menstruation was regular. Physical examination showed a very corpulent young woman weighing 214 pounds, with an especially marked adipose layer over the hips. The distribution of the body hair was normal. There was hyperplasia of the thyroid gland with increased vascularity. There was a slight systolic murmur at the apex of the heart; the pulse was 124; the blood pressure 128/60; basal metabolism minus 8 per cent. The radiograph showed a normal sella turcica. The findings in the glucose tolerance test as shown by Chart II, middle curve, suggest the presence of a mild diabetes.

Case III. A single woman, 32 years of age, of retarded mental development. There was no history of any previous disease. The patient reported that she had had sugar in the urine for the preceding two years. She was very fond of sweets, and had an enormous appetite. She sometimes had polyuria. She had some pruritus vulvae. She had lost no weight. She became stout and flabby after puberty. The menstrual periods were irregular. Physical examination showed an obese young woman 5 feet 6 inches in height, weighing 190 pounds. The blood pressure was 115/75. Her expression was rather listless, features were coarse, eyesight poor. The skin over the face and neck was very red. Her breasts were undeveloped. The distribution of pubic hair was of the male type. There was no glycosuria. The glucose tolerance test gave a record which showed that this was a borderline case of diabetes. (Chart II, lower curve.)

Case IV. A girl 11 years of age. Her only previous illness had been several attacks of tonsillitis. She came to the clinic because of headache and nervousness. Physical examination showed an obese little girl, weighing 120 pounds, of sluggish mentality, with no other abnormal physical findings. The x-ray plate showed the sella turcica to be slightly smaller than normal. There was no glycosuria. The glucose tolerance test showed a slight decrease in carbohydrate tolerance; that is, like the preceding case, this was a borderline case of diabetes.

Case V. A married woman, 25 years of age. There was no history of any childhood diseases but she had had pneumonia, grippe, tonsillitis and influenza. She complained of a continuous headache and pains in the back, of 8 years duration, always increased at the

CHART II

Glucose tolerance curves in cases of hypopituitarism, showing the presence of definite diabetes (upper curve), mild diabetes (middle curve) and prediabetic stage (lower curve).

menstrual periods. The menses were regular but she had severe dysmenorrhoea. During the preceding year she had gained 20 pounds and 40 pounds the year before. Physical examination showed a very obese woman 5 feet 3 inches in height and weighing 200 pounds. There was marked hypertrichosis of the face and chest. The axillary hair was normal, the hair distribution on the pubis was

of the male-type. The thyroid was enlarged. The heart was normal, the blood pressure 126/86. The x-ray plate showed the sella turcica to be enlarged. The blood Wassermann test was negative. The blood urea was 15 and uric acid 4 mg. per 100 cc. There was no glycosuria. The glucose tolerance test suggested a decreased carbohydrate tolerance—a mild type of diabetes.

Among these five cases, each of which showed clinical signs of hypopituitarism, one was definitely a case of diabetes, one a mild type of diabetes, and three were in a prediabetic stage. We can definitely say that there is decreased carbohydrate tolerance in all five of these cases in spite of the fact that theoretically, because of the hypopituitarism, there should be an increased tolerance for carbohydrates. Van Noorden (3) called attention to such a condition when he said: "Recently cases have been shown which are of the hypopituitary type (for instance hypophyseal tumors with degeneration adiposo-genitalis) in which glycosuria is manifest and even diabetes mellitus appears." The observations here reported confirm Van Noorden's statement, but they unfortunately give us no information regarding the etiology of diabetes—I can not but feel that the diabetes which is present in hypopituitary disorders is but a coincidence —and that the hypopituitarism has nothing whatever to do with it. These patients may be born with a hypoinsulogenic function; and thus if they happen to strain this weakened function by overeating, which seems to have happened in all these cases, for they are all markedly obese, there is nothing to stop them from breaking down completely the already impaired insulogenic function unless the danger is discovered early and the downward progress arrested. These cases are of interest, however, in that they serve to emphasize the danger of accepting any apparent physiological rule as a final, all-inclusive dictum.

BIBLIOGRAPHY

1. Engelbach, W.: Classification of disorders of the hypophysis. This Journal, 1920, 4, 347-365.
2. Sachs, E., & MacDonald. M. E.: Blood sugar studies in experimental pituitary and hypothalmic lesions, with a review of literature. Arch. Neurol. & Psychiat. (Chicago), 1925, 13, 335-368.
3. Van Noorden : Die Zuckerkrankheit und ihre Behandlung (Berlin), 1920, 7 ed., p. 99.

STUDIES ON VIGOR. VI. THE EFFECT OF STARVATION ON THE SPONTANEOUS ACTIVITY OF CASTRATED RATS

R. G. HOSKINS

From the Laboratory of Physiology, Ohio State University

COLUMBUS

In a previous report (Hoskins, 1925-a) it was shown that castration in rats results in a marked depression of spontaneous activity. Similar results have been obtained by Allen (1925) at the Phipps Psychiatric Clinic of the Johns Hopkins Hospital. An animal deprived of its testes at about the time of puberty manifests throughout what would otherwise have been its most vigorous period a degree of activity corresponding to that of the early senile phase.

Such observations lend plausibility to the theory that a part of the inactivity of old age is due primarily to lack of testicular hormone. Whether this inactivity is due merely to lack of some stimulating element or to secondary structural changes is by no means clear. The problem is under investigation in our laboratory. It is significant that castrated rats, like castrated farm animals, show no obvious decrease in actual strength, though adequate determination of endurance are lacking.

It is not improbable that deficiency of testicular hormone may play a significant role in clinical conditions marked by lack of vigorous initiative. While "hypogonadism" can not be excluded from the endocrine phantasmagoria, neither can it definitely be included. Although there is no respectable basis for dosing patients with dried testicle, the subject of clinical gonad deficiency is a proper one for careful study.

In connection with investigations of the effects of castration, various attempts have been made toward ameliorating the characteristic depression. An initial study of testicle grafting gave completely negative results (Hoskins, 1925-b). These studies are being continued in the hope that a more adequate technic may be evolved and give positive effects.

It was thought that the castration depression might involve a vicious circle: that the inactivity would lead to partial clogging of active body tissues with fat, which condition in turn would tend to augment the inactivity. If this were true a period of starvation might be followed by a phase of augmented vigor such as Carlson has reported in man (1914). It was believed that greater activity would in all probability result during the period of fasting, if for no other reason, because the gastric hunger contractions would serve as a continuously acting stimulus. Powelson (1925) has shown by direct observation in this laboratory that there is a considerable degree of correlation in the rat between gastric peristalsis and spontaneous movements.

Fig. 1. Activity of starved castrated rats as manifested by turning revolving cages one foot in diameter; 7 days' preliminary period, 6 days inanition period, and 11 days post-inanition period on full diet. Averages for fifth and sixth days based on six animals, only.

In the experiments herein reported ten castrated rats ranging in age from 221 to about 450 days were subjected to starvation, six for six-day periods and four for four days. They were continuously supplied with water. Their spontaneous activity was determined by the revolving cage method used in previous researches (Durrant, 1924, 1925; Hoskins, 1925).

For a week previous to the starvation period the average cage activity of the group, as shown in the accompanying table and figure, ranged from approximately 1,744 to 2,280 yards daily. During the starvation period the activity reached approximately three times that of the initial period. In two of the six animals starved for six days the maximum activity was

Animal No.	DAYS BEFORE STARVATION							STARVATION PERIOD—DAYS						DAYS AFTER STARVATION										
	7	6	5	4	3	2	1	1	2	3	4	5	6	1	2	3	4	5	6	7	8	9	10	11
111	1020	780	1690	730	1760	720	1570	1450	3220	3500	5190	7820	6070	1350	3690	1810	2850	2780	2950	2600	2460	3700	1880	2890
118	2890	2050	1650	3100	2560	6050	1610	1080	3660	6510	8170	10060	6610	1530	2610	7020	1110	2810	1090	4090	1890	1880	3170	4160
159	730	1150	850	550	780	770	1120	1510	1990	2280	3121	5600	3540	2160	2910	3200	2730	3070	2300	1930	1560	2770	2670	1480
216	910	1150	1710	570	1190	1360	1110	1610	2650	2890	5100	5580	5910	1680	2100	2470	2830	2700	2130	1680	1220	2740	2560	1030
273	1160	770	870	1110	1050	810	1080	1320	1590	2500	3270	3020	2360	1730	20	10	0	10	80	150	150	130	420	20
280	620	880	750	1170	790	760	900	1160	1310	1520	2330	1110	1930	2150	1220	1350	1610	2010	1030	900	1630	1820	580	720
10	1870	2350	1610	1300	3770	1510	1820	1600	1540	1050	3620			760	1110	530	1500	1020	2090	1680	500	760	1250	1250
175	4150	5080	1270	3830	5080	1040	3760	1680	3910	2220	5310			2710	2570	1590	2600	1850	2330	1990	2600	2600	1820	2770
181	3050	3210	3160	1170	1010	3620	2080	3500	5230	6410	6690			3080	3290	3070	1220	2870	2710	3610	4720	3280	2020	1620
197	2630	2390	1650	1420	1810	2800	1460	2310	2930	3100	3820			2270	1890	2170	1800	1920	2000	1690	1750	1810	2290	1700
Average	2006	2011	1821	1825	2280	2247	1711	2391	2797	3304	4697	6082	1897	2512	2163	2321	2110	2104	2323	2011	1848	2140	1866	2163

recorded on the sixth day; in three, on the fifth day, and in one, on the fourth day. In case of those starved four days only the maximum activity in each case occurred on the fourth day. The activity was tabulated for a period of eleven days after the animals were returned to full rations.* The average activity of the whole group returned almost to normal on the second day after feeding was resumed. A study of the individual records, however, indicates that this average serves to mask two opposite tendencies. In four cases the activity level was considerably higher for several days than during the initial period. In three other cases it was as definitely lowered. In the latter cases it is probable that the starvation was carried to a physically detrimental length. Indeed, in case of four normal control animals similarly subjected to inanition death resulted on the third or fifth days.

A further study with detailed observations on weight loss and recovery is in progress.

SUMMARY

Ten castrated rats were subjected to four or six days' starvation. Their spontaneous activity as registered by the revolving cage method was augmented about 200 per cent. In four cases the increased activity persisted for several days after full feeding was resumed, whereas in three a depression, probably due to resulting physical debility, ensued.

BIBLIOGRAPHY

Allen, F. H   1925   Personal communication.
Carlson, A. J.: 1914   Am. J. Physiol. (Balt.), 33, 95.
Durrant, E. P.: 1924.   Am. J. Physiol. (Balt.), 70, 344.
    1925.   This Journal, 9, 221.
Hoskins, R. G.: 1925.   (a) Am. J. Physiol. (Balt.), 72, 324.
    1925.   (b) This Journal, 9, 277.
Powelson, M. H.: 1925.   Science, 62, 247.

---

* Our stock ration consists of whole wheat flour, 62.5%; casein, 15%; skim milk powder, 15%; CaCO₃, 1.5%; NaCl, 1%; oil or fat, 5%; with addition of cod liver oil, fresh cabbage and corn.

A NOTE ON THE EFFECT OF ADRENALIN UPON STRIPS OF EXCISED PREGNANT HUMAN UTERUS

CHARLES M. GRUBER

From the Department of Pharmacology, Washington University Medical School

ST. LOUIS

A large number of studies (1) have been performed to determine the excitability of excised strips of pregnant and non-pregnant human uteri. To Rübsamen and Kligermann (2) credit should be given for having been the first to observe the effect of suprarenalin upon excised strips of both gravid and non-gravid human uteri. They noted suprarenalin to produce contraction or increased tonus in both types. Two years later, without apparent knowledge of previous work having been done upon the human uterus, Gunn (3) studied the effect of adrenin upon strips of excised uteri of rabbits, cats and guinea pigs. He also studied the effect of this drug in four strips of excised human Fallopian tubes and in one instance upon the uterus. He found adrenine to produce contraction, i. e., increased tonus, in both organs and therefore concludes "unless, however, the human uterus has a still different type of sympathetic innervation from that of all the animals which have been examined, the probability is that adrenine will have a motor effect on the pregnant human uterus, and that, therefore, the use of sympathominetic substances in labor is justified."

In 1915 Lieb (4) reported the effect of epinephrine upon a strip of excised non-gravid human uterus and its effect upon strips of "parturent" human Fallopian tubes. From these experimental observations he believes the conclusion to be justified that the sympathetic innervation of the human uterus is always motor in quality.

Because of these latter conclusions an attempt was made to confirm if possible Rübsamen and Kligermann's (2) results upon excised normal gravid human uteri.

METHOD

The strips of uteri used were narrow sections cut from the walls of normal pregnant human uteri when Caesarian sections were performed in cases where there existed a disproportion in size of the fetus to the pelvic outlet.* Three such strips were studied. These strips were fresh and used shortly after removal. They were immersed in warm 38.5°C Locke's solution, through which a constant stream of oxygen flowed. The methods for recording, etc., were essentially the same as those used by Kehrer (1b). The time interval was thirty seconds. Adrenalin chloride (Parke Davis & Co.) was used. This was added directly to the fluid which bathed the muscle.

Figure 1   Excised strip of a normal pregnant uterus at term. The up stroke represents contraction, the down stroke relaxation. 1, adrenalin chloride was added to make a 1:200,000 solution bathing the tissue.

RESULTS

Our results on the effect of adrenalin on excised strips of pregnant human uteri confirm the finding of Rübsamen and Kligermann (2). In the three cases thus studied 0.5 ml. adrenalin chloride 1:1000 added to the Locke's solution, making a 1:200,000 adrenalin chloride dilution, caused a marked increase in the tonus of the pregnant uterus. Figure 1 is typical of the results obtained from all such uteri. In this and in the other

cases the increased tonus lasted for a long time. Weaker solutions appeared to have a similar effect though less in degree.

DISCUSSION

It has been demonstrated by Cannon and his coöperators (5) that the adrenal secretion is stimulated by pain, excitement, etc. Cannon and Gray (6) demonstrated decreased coagulation time of the blood after the injection of small doses of adrenalin. Similar results were obtained by Cannon and Mendenhall (7) upon stimulation of the splanchnic nerves with the adrenal glands intact and upon stimulation of the sciatic nerve (8). That adrenalin alleviates fatigued muscle was demonstrated by Cannon and Nice (9) and by Gruber (10). Upon the basis of these findings we may assume that if there is increased secretion of adrenalin during labor, it would produce increased tonus of the uterus, increased force of contraction of the abdominal muscles and decreased coagulation time of the blood during and after labor, and we agree with Gunn (3) that the use of sympathominetic substances in labor is justified.

SUMMARY

The effect of adrenalin was studied upon strips taken at the time of Caesarian section from three pregnant human uteri. In each case our results confirm the findings of previous investigators in that it increased the tonus of the muscle.

BIBLIOGRAPHY

1. (a) Franz: Ztschr. f. Geburtsh. u. Gynæk. (Stuttg.), 1904, 53, 361.
   (b) Kehrer: Arch. f. Gynæk. (Berl.), 1907, 81, 160.
   (c) Rübsamen & Danziger: Ztschr. f. Geburtsh. u. Gynæk. (Stuttg.), 1911, 69, 656.
   (d) Rübsamen & Perlstein: Arch. f. Gynæk. (Berl.), 1912, 95, 105.
2. Rübsamen & Kligermann: Ztschr. f. Geburtsh. u. Gynæk. (Stuttg.), 1912, 72, 27; abst., Ztschr. f. Biochem u. Biophys., 1912, 14, 602.
3. Gunn: Proc. Roy. Soc., 1914, B. 87, 551.
4. Lieb: Am. J. Obst., 1915, 71, 217.
5. (a) Cannon & de la Paz: Am. J. Physiol. (Balt.), 1911, 28, 64.
   (b) Cannon & Hoskins: Ibid., 29, 274.
   (c) Cannon: Ibid., 1914, 33, 358; Ibid., 1919, 50, 399; etc.
6. Cannon & Gray: Ibid., 1914, 34, 232.
7. Cannon & Mendenhall: Ibid., 243.
8. Cannon & Mendenhall: Ibid., 251.
9. Cannon & Nice: Ibid., 1913, 32, 144.
10. Gruber: Ibid., 1914, 33, 335; Ibid., 34, 89; Ibid. 1917 43; 530; Ibid., 1918, 45, 302; Ibid., 1922, 61, 475; Ibid., 62, 438; etc.

STUDIES ON THE OESTROUS CYCLE IN THE RAT.
I. THE EFFECT OF THYROIDECTOMY

MILTON O. LEE

From the Department of Physiology, Ohio State University

COLUMBUS

The thyroid gland has long been considered to have a rather intimate functional relationship with the female gonads. This opinion has been held largely on account of the swelling of the thyroid at puberty, menstruation, pregnancy and the menopause, and because of the fact that Graves' disease is more common in women than in men (Gley, 1917; Vincent, 1925). Up to the present definite experimental evidence establishing or refuting such a relationship has been lacking, due largely to the fact that we have had no adequate method of determining slight variations from normal ovarian function. Hammett's recent statistical study (1925) indicates that the assumed importance of the thyroid-ovarian relationship has been overestimated.

Evans and Long (1921, a) have reported that thyroidectomy in rats affected neither the onset of puberty, nor the lengths of the oestrual cycles. They also reported (1921, b) that feeding of fresh thyroid gland substance had no disturbing effect upon the oestrual cycles.

In view of the interest and importance of this question and of the fact that many of the thyroidectomized rats in the series of Evans and Long showed regeneration of thyroid tissue, thus vitiating their results, it was thought desirable to repeat the work, making sure of an actual hypothyroidism of the animals.

MATERIAL AND METHODS

Eighty female albino rats of from 34 to 150 days were selected from the general colony. Eighteen of these, selected at random, were used as controls for this and other experiments in progress at the same time. Fifteen of these controls remained in good condition throughout the duration of the experiment,

and are reported in detail in Table 1. Three controls developed a respiratory infection and were discarded.

A sham operation, in which the thyroid glands were exposed and touched, but left intact, was performed upon five other control rats. The results from this procedure will be discussed below.

Thyroidectomy was performed on the remaining fifty-seven rats. Of this number some few died under ether anesthesia or from the effects of the operation. Some developed poor health during the course of the experiment and were discarded. Some others were found at autopsy or biopsy to have regenerated considerable thyroid tissue. These were discarded from the thyroidectomized series and are reported as a separate group in Table 3.

The twenty-nine cases forming the basis of this report remained in good health throughout the observation period and showed little or no regeneration of thyroid tissue. Seven animals of the twenty-nine were thyroidectomized before puberty, at the ages of 38, 40, 41, 39, 52, 56 and 34 days, respectively. The ages of the remainder at the time of operation varied from 90 to 150 days.

All animals were kept under the same environmental conditions in a well ventilated room, in which the temperature varied not more than four degrees (average eighteen degrees centigrade) during the whole period of five to six months. Four or five rats were confined to a cage 20x12x10 inches. A diet containing abundant mineral salt and vitamin constituents was fed, the food being kept before the rats at all times. This food, a modified McCollum mixture, contained the following constituents per hundred pounds:

Whole wheat flour.................................62.5 lbs.
Skim milk powder................................15.0 "
Casein ....15.0 "
$CaCO_3$ .... 1.5 "
NaCl .... 1.0 "
Lard plus cod liver oil......................... 5.0 "

In addition, fresh cabbage or lettuce and corn were fed weekly.

The health condition of this series was given especial attention. The bedding was changed often; the rats were kept

free from vermin; the teeth were kept at proper length, and undried food was fed on occasion. All rats reported upon maintained normal growth and body weight and remained to all appearances in good health. These details are mentioned because it is our experience that any condition of undernutrition, disease, crowding of animals in small cages, or extreme variation of temperature upsets the normal oestrual rhythm. The physical condition of a female rat is quite accurately reflected in the oestrual cycles. Any infection, inanition or other abnormal condition is quickly shown by a lengthened dioestrum or rest interval. In fact, such a halting of the normal rhythm often indicates the incidence of infection before there is any loss of weight or other evidence of it.

In the removal of the thyroids from the experimental rats a careful though not elaborate technic was followed. The animal was anesthetized with ether and tied out on a small board under a binocular microscope magnifying ten diameters. The thyroids were then exposed. Fine silk ligatures were placed around the vessels entering each thyroid lobe at the anterior and posterior ends (superior and inferior thyroid arteries). The mass of thyroid tissue was then carefully separated from the capsule by the use of a flexible needle, care being taken not to injure the recurrent laryngeal nerve which runs along the mesial border of each lobe. If this is seriously injured by cutting or undue traction the animal often develops gasping or gagging, takes no food and dies in a day or so. If the operation is done carefully bleeding is slight, healing rapid and mortality low.

The parathyroids were located in each case and at least one left in situ. In some cases the parathyroid was left with circulation intact, the thyroid being teased from around it; in others the parathyroid was removed with the thyroid, identified, teased out and replaced. In no animal of this series was any symptom of parathyroid deficiency noted. In many, evidence of thyroid deficiency became apparent in the loss of fine, soft hair, and the growth of coarse, thin hair, much as in senility.

At the end of the experiment all of the thyroidectomized rats were autopsied or biopsied. All tissues suspected to be

thyroid were removed, fixed and sectioned. Eleven out of forty animals were found to have regenerated thyroid tissue to such an extent that they were discarded from the series. Nine of these eleven which showed regeneration had been thyroidectomized before 50 days of age, indicating a greater possibility of regeneration in young than in adult rats. No hesitancy is felt in considering the twenty-nine animals in Table 2 to be definitely lacking in thyroid secretion.

The oestrual rhythm was followed by means of the smear method developed in Stockard and Papanicolaou (1917) and by Long and Evans (1922). By this method the cycle is divided into five periods, distinguished by the varying character and combination of cell types, in the vaginal fluid, as determined by microscopic examination. The five periods are: preparation for oestrus (stage I), oestrus (stage II), post oestrus (stage III), repair (stage IV) and rest or dioestrum (stage V). It has been found that if the rats are used to being handled the procedure of withdrawing samples of vaginal fluid for examination affects in no wise the oestrual rhythm. The various stages present such different microscopic pictures that no difficulty is experienced in distinguishing them.

OBSERVATIONS AND DISCUSSION

Daily determinations of the stage of oestrous in all animals were made by the method given above. In the case of the control series observations were made from October to the following June. The twenty-one experimental animals which had arrived at puberty some time before thyroidectomy was performed showed in this period before operation oestrual cycles of exactly the same average length as the control series, viz., 4.8 days.

In thirteen of the twenty-nine animals of the experimental series the oestrual rhythm was disturbed for one or two cycles immediately following thyroidectomy, these cycles being considerably lengthened (varying from eight to sixteen days).

It is highly probable that this effect is not to be ascribed to thyroid deficiency per se, but rather to the severe trauma and, in some cases, slight infection. This is further borne out by the fact that four of the five control animals which were traumatized showed a similar lengthening of the cycle immediately after

TABLE 1

Showing Lengths of Oestrous Cycles, in Order of Occurrence, in Control Series

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS
275	5,6,4,4,5,4,4,5,5,4,4,5,5,7,6,4,6,5,6,4,5,6,5,5,4,4,5,5,3,4,5,5,3,4,4,5,5,4,4,5,5,3,4,4,5,5,4,4,5,4,4,5,5,4,4,5,5,4,5,5,4,5,5,5	52	249	4.8
276	6,5,5,6,5,5,3,4,4,5,6,5,4,4,5,6,5,4,5,5,4,5,5,6,5,5,4,4,5,5,5,4,6,5,4,4,5,5,5,4,5,5,5,5,6	49	240	4.9
222	5,5,6,5,4,4,5,5,3,6,4,4,5,6,5,5,4,4,5,4,5,6,5,4,6,6,4,5,5,4,5,5,3,6,4,5,5,5,4,5,5,3,6,4,5,5,5,4.	51	246	4.8
284	5,6,4,4,5,6,6,5,5,5,4,4,6,7,5,5,6,6,5,5,5,5,5,5,4,6,5,5,4,4,5,6,5,4,6,5,5,4,4,5,4,5,6,4,5.	49	245	5.0
287	5,4,6,4,5,6,5,4,4,5,5,4,4,5,5,3,6,4,4,5,5,3,6,6,7,5,5,3,5,4,4,5,5,4,5,5,4,5,5,4,5,5,4,5,5,4,5,5,4,5,5,5.	51	248	4.9
288	5,4,4,5,5,5,4,4,6,5,5,4,4,5,5,3,5,5,6,4,4,5,5,5,5,6,5,5,4,4,5,5,4,5,4,5,5,4,5,5,4,5,5,6,5,5,6,5,4,5	52	250	4.8
297	5,6,3,6,4,4,6,5,5,4,4,5,5,3,5,5,6,4,4,5,4,5,5,5,4,4,5,5,4,5,4,5,5,4,5,5,5,5,4,4,5	50	241	4.8
208	4,5,5,4,4,5,5,5,4,4,5,5,5,4,4,5,5,3,4,4,5,5,5,4,4,5,5,6,5,5,4,4,5,5,5,6,4,4,5,5,5,4,5,5,4,5,5,6.	51	245	4.8
113	4,1,5,6,5,4,4,5,6,4,4,4,4,5,5,5,5,5,5,5,5,4,4,5,5,4,5,4,5,4,4,5,5,3,5,6,5,5,5,5	51	244	4.8
564	5,4,5,5,4,4,6,4,5,3,5,5,6,5,5,6,5,5,5,7,5,4,4,4,5,5,5,5,6,6,5,5,5,5,5,4,4,5,5,4	50	243	4.9
565	5,6,6,5,7,5,4,6,4,5,5,4,5,5,4,5,5,6,5,5,5,5,5,5,4,5,4,5,5,5,5,5,4,5,5,5,6.	19	243	4.9
566	6,4,6,5,5,5,4,5,5,4,5,5,4,5,5,5,5,5,5,4,5,5,4,5,5,5,5,5,5,4,4,5,5,5,5,5,6,5.	51	248	4.9
586	4,4,5,4,4,5,5,5,6,6,5,4,6,5,4,4,4,4,6,5,4,4,6,5,4,4,4,4,5,5,5,4,5,5,5,4,5,5,4,4,5,4.	52	246	4.7
587	5,5,5,5,4,5,5,5,5,4,4,4,5,5,5,5,4,4,5,5,5,4,1,5,4,5,5,4,6,4,4,5,6,4,4,5.	51	242	4.7
588	5,5,3,5,3,5,4,4,5,5,5,5,1,5,5,5,5,4,4,5,5,5,5,6,4,4,5,5,5,6,4,4,5,5,5,5,4,5,7,4,5.	51	245	4.8
Totals..		760	3,675	
Average		50.7	245	4.8
Standard deviation..			...	±0.1

Showing Lengths of Oestrus Cycles in Thyroidectomized Rats

RAT NO.	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS	AGE AT FIRST OESTRUS DAYS	REMARKS
102	4,5,1,6,7,7,1 5,7,7,1,7,0,5,4,5,5,4,7,8,1,6,6	23	127	5 5		
108	5,5,0,6,1,4,5,7,7,10,8,7,8,7,6,5,6,7,7	19	121	6		
125	7,5,0,7,1,8,5,4,0,7,5,0,7,8,6,6,0,5,6,5,5	20	122	6 1		
196	(13),5,6,3,5,6,6,5,1,4,5,6,0,5,5,5,5,5,6,8,5	21	113	5 4	76	First oestrus 15 days after thyroidectomy
613	6,7,1,4,5,1,6,1,6,0,5,5,1,0,5,7,5,4,4,7,7	25	132	4 3	62	First oestrus, 21 days after thyroidectomy
884	*11|[8]|[7],1,7,8,8,8,12,7,6,0,4,7,7,7	13	91	7 0	53	First oestrus, 19 days after thyroidectomy
880	*10|[5]|[6],7,0,8,5,5,7,1,5,6,0,0,6,7, .	14	84	0 0	61	
915	*8|[8],[6],0,5,5,6,4,6,10,7,5,0,9,8,7	13	84	0 5	60	
555	(12),5,1,4,5,5,0,0,6,0,5,0,6,5,6,5,5,5,5,4,5	22	117	5 3	57	
165	(11),6,5,6,9,13,7,5,8,7,4,4,5,5,10,6,6,6,9,8,7	20	111	7 0		
215	(17),3,4,5,8,8,7,5,6,7,7,6,7,8,7,6,0,6,7,5,6,6	20	131	6 1		
257	5,11,5,5,5,6,5,5,5,7,8,4,8,7,10,6,6,7,5,5,5,5,5,7,	24	147	6 1		
208	(8),4,5,10,7,1,5,0,0,5,0,6,0,5,7,4,12,8,7,9,7,1,6	21	133	6 3	60	
553	(16),(12),7,5,5,4,5,1,5,4,5,5,7,5,5,5,8,7,6	17	96	5 0		
301	6,6,10,8,10,7,0,7,7,7,7,5,5,5,5,0,0,0	20	138	6 9		
578	(0),5,5,5,5,5,8,5,4,7,0,8,0,6,1,6,5,6,0,10,6,6,7	21	141	6 9	89	First oestrus, 20 days after thyroidectomy
597	(0),8,1,6,6,6,4,7,5,5,0,1,5,6,6,4,7,0,5,5,6,7	24	133	5 5	77	
599	(0),0,8,5,5,9,0,0,7,8,6,6,7,0,7,7,5,5,6,5,7	22	145	6 6	71	
783	6,5,5,5,0,7,8,6,6,6,7,7,7,7,5,5,6,7,6,7	23	145	6 3	54	
828	5,0,5,5,0,1,4,7,5,6,6,5,5,5,4,5,3,5,4,6,7,6,5,7	25	132	5 3	58	
838	(12),7,7,4,5,1,5,7,6,5,10,5,5,5,5,4,0,4,4,5,5,5,4,6,5	23	125	5 4	61	
844	*(0)|[5]|[7],5,12,5,5,6,1,0,4,1,5,5,5,6,6,6,5	16	89	5 4	68	
816	(8),5,2,5,6,5,9,6,5,5,4,0,5,5,5,5,5,6,6,4,6,5,5	24	129	5 1	62	First oestrus, 20 days after thyroidectomy
700	6,4,5,4,5,4,1,1,5,8,7,4,5,7,1,4,7,5,0,1,5,5,5,6	26	133	5 1	66	First oestrus, 2 days after thyroidectomy
851	(11),7,9,0,6,1,5,5,3,6,5,5,6,5,6,1,4,5,5,6,5,3,0	23	120	5 5	53	Thyroidectomized on day of first oestrus
862	*12|[0]|[8],8,6,6,6,11,7,5,6,5,5,6,7	11	91	6 5	72	First oestrus, 3 days before thyroidectomy
861	*10|[7]|[15],9,6,5,9,10,5,3,1,1,5 6,5,5,1,5,6,0,6,7	18	103	5 7	59	
874	*12|[7]|[15],0,5,0,6,7,5,4,4,5,6,5,4,6,5,6,6,0,6,7	21	113	5 4	55	
878	[10],[17],[10],6,7,7,0,5,5,0,5,0,5,9,7,6,5,5,6,7,5,	19	112	5 9	80	
Totals		591	3,197			
Average length of cycle				5 9		
Standard deviation				±0 5		

Parentheses, ( ), around numbers indicate lengthened cycles immediately following thyroidectomy. These figures were not used in the calculations.

An asterisk, *, indicates that the animal was thyroidectomized some time before puberty.

Brackets, [ ], around numbers indicate cycles immediately following the first establishment of oestrus at puberty. In each such case the figures for the first three cycles were not used in the calculations.

the sham operation, followed by a re-establishment of the normal rhythm. Experience in adrenalectomy also indicates that in all such cases of operative trauma the cycles are temporarily arrested in the dioestrum.

These abnormally long cycles immediately following thyroidectomy are indicated in the table by parentheses () and were not used in calculations to obtain the average lengths. In eight cases there was no, or only a very slight, arrest of the rhythm after the operation. In all of the thyroidectomized animals reported upon the rhythm was re-established, but the cycles did not return to normal length. In each case the cycles became longer on the average, and less regular, as may be seen by examination of Table 2. This irregularity and lengthening was more noticeable in some rats than in others.

In eleven thyroidectomized rats which had regenerated much thyroid tissue, and which are treated separately, this irregularity was much less marked. In fact, several of them showed an average length of cycle nearly the same as that of the controls. It is significant that this regularity was only gradually recovered, presumably coincident with the regeneration of the thyroid. See Table 3.

In every case of a lengthened cycle the dioestrum or rest interval was the period involved, occupying from three to fifteen days as against two days in the average normal cycle. None of the other stages of the cycle showed any detectable abnormality. Thyroidectomized females in stage II showed the same heat reactions when placed with a male as did their normal controls.

In the thyroidectomized series a total of five hundred and ninety-four cycles, or an average of about twenty-one per animal was followed, giving a total average length of 5.9 days per cycle as against 4.8 days for normal rats. In obtaining this average both the lengthened cycles immediately following thyroidectomy and the first three cycles following puberty were omitted in the calculations. The first few cycles in a young rat are very often irregular (Long and Evans, 1922).

The seven animals which were thyroidectomized from three to twenty-nine days before the establishment of oestrus showed no postponement of puberty. The ages at which this occurred in these animals were well within the normal limits.

TABLE 3

Showing Lengths of Cycles in Thyroidectomized Rats in Which at Autopsy Regenerated Thyroid Tissue was Found

RAT NO	LENGTHS IN DAYS OF SUCCESSIVE CYCLES	TOTAL NO. CYCLES	TOTAL NO. DAYS	AVERAGE LENGTH OF EACH CYCLE DAYS	AVERAGE LENGTH OF LAST 10 CYCLES DAYS
829	(10),7,0,6,5,7,8,6,5,7,0,6,5,5, 4,6,5,5,1,6,5,5,4,1	24	132	5 5	4 8
912	[7],[9],[0],7,7,6,7,5,8,0,6,5,6,6, 5,4,1,6,5,5,5,4,5,1.	21	116	5 5	4 7
911	[11],[8],[8],9,6,0,7,5,7,0,1,6,5,5, 5,6,0,4,6,4,5,4,4,5	21	115	5 5	4 9
913	[7],[10],[7],0,8,8,6,7,0,5,5,7,0, 5,4,5,6,5,5,4,6,1,5	20	112	5 6	4 8
008	[8],[0],[7],0,5,7,7,0,8,5,0,6,5, 5,1,5,5,5,5,4,0,4,5 •	20	108	5 1	4 7
877	[0],[8],[6],7,8,0,0,5,0,5,5,7, 6,5,4,5,5,4,5,1,4,5.	19	102	5 4	4 7
832	(11),7,0,7,5,4,5,7,7,0,6,0,5,5,5,4,0, 4,6,5,5,5,5,1,6,5,4	25	135	5 4	4 9
840	[8],[7],[7],6,5,8,7,7,6,7,5,1,6,5, 5,6,1,5,5,1,4,4,5,5	21	112	5 3	4 6
909	[13],[8],[5],7,5,5,6,7,5,8,5,6, 4,1,6,5,5,4,1,6,5	19	101	5 3	4 9
945	[10],[7],[0],5,6,0,3,5,5,4,5,6, 5,6,1,5,5,6,0,4,5,5	19	95	5 0	5 0
847	(11),7,0,6,5,6,0,7,0,5,1,5,5,0,1, 5,5,5,1,5,5,5,6,4,5	21	127	5 3	4 9
	Totals	233	1255		
	Average length of cycles (days).			5 1	4 8
	Standard deviation			±0 1	±0 1

For explanation of symbols see table 2.

The unoperated control animals showed normal cycles throughout the time of observation. The average duration of these cycles (4.8 days) and the lengths of their component stages correspond closely to data from other rats in this laboratory, and to figures given by Long and Evans (1922).

After making due allowance for the effect of operative trauma a difference of one day in the average lengths of cycles of control and thyroidectomized animals seems too great and too consistent to be accounted for by chance. The first possible explanation that offers itself is, of course, that normally, the thyroid exercises a stimulating action on those cells of the ovary that elaborate a hormone which is responsible for the cyclic changes of the reproductive tract. That the ovary does produce such a hormone is rather convincingly shown by both the effects of ovarian extirpation and of the administration of ovarian extracts (Allen and Doisy, 1923; Doisy, et al., 1924; Frank, et al., 1925). According to this view thyroidectomy removes the rather constant stimulus to the ovarian cells. As a result, the time between the production of successive physiologic doses of ovarian hormone is increased, and the dioestrum of the cycle is correspondingly lengthened. The evidence as yet is deemed insufficient to justify a definite statement that such is the case. In fact, the indications are that in this interaction the ovary is the stimulating gland. That is, the ovarian hormone, besides initiating the growth changes of the genital tract, causes increased activity in the thyroid gland. This is shown by the enlargement of the thyroid at puberty, menstruation and pregnancy (Marine, 1923; Daly and Strouse, 1925).

Another possible explanation is that the thyroid through its action on other body cells has an indirect effect upon the ovary. It has been found, as will be reported in a subsequent paper of this series, that activity affects markedly the length of the dioestrum. Female rats kept in activity cages, in which the voluntary activity is much greater than when in stationary cages, almost invariably show very short dioestrual intervals. Incomplete data from this laboratory indicate that in a considerable proportion of cases, thyroidectomized animals in recording cages show considerably less than normal spontaneous activity (Hoskins, 1925). It is suggested that ovarian activity

varies roughly with the general activity of the animal, and that the effect of thyroidectomy on the oestrual cycle is a secondary one, the primary effect being upon general metabolism, bodily activity and vigor.

SUMMARY

1. A study of oestrual cycles following thyroidectomy was made in forty rats, eleven of which regenerated considerable amounts of thyroid tissue.

2. In case of the twenty-nine animals in which complete or nearly complete ablation was secured the first and sometimes the second cycle following the operation were often much lengthened. This is interpreted, however, as due to trauma, or slight infection, as it also occurs in rats upon which a sham operation is performed.

3. The succeeding cycles, over a period of five months, showed an average lengthening of about one day above those in normal controls under the same environmental conditions.

4. The eleven animals which regenerated much thyroid tissue showed at first a lengthening of the cycles, and then a gradual return to the normal length.

5. Thyroidectomy at an age considerably before the establishment of the oestrual rhythm seemed to have no effect on the age of puberty.

6. Possible explanations for the lengthened dioestrum following thyroidectomy are suggested: (a) that normally the thyroid exercises a stimulating influence on the ovary, and that removal of this stimulus allows the cycle to be lengthened; (b) that ovarian activity varies with the general bodily activity and that thyroidectomy affects the oestrual cycle through its effect upon metabolic processes.

It is a pleasure to acknowledge indebtedness to Professor R. G. Hoskins for generous advice and criticism.

BIBLIOGRAPHY

Allen, E. & Doisy, E. A.: 1923. An ovarian hormone. J. Am. M. Ass. (Chicago), 81, 819 (Sept. 8.)

Daly, P. A., & Strouse, S.: 1925. The thyroid during pregnancy. J. Am. M. Ass. (Chicago), 84, 1798 (June 13).

Doisy, E. A., Ralls, J. A., Allen, E. & Johnston, C. G.: 1924. The extraction and some properties of an ovarian hormone. J. Biol. Chem. (Balt.), 61, 711 (Oct.).

Evans, H. M. & Long, J. A.: 1921 (a). The effect of thyroidectomy on the

oestrus cycle of the rat. Proc. Am. Ass. Anat., Anat. Rec. (Balt.), 21, 61.

Evans, H. M. & Long, J. A.: 1921 (b). The effect of thyroid feeding on the oestrus cycle of the rat. Proc. Am. Ass. Anat., Anat. Rec. (Balt.), 21, 61.

Frank, R. T., & Gustavson, R. G.: 1925. The female sex hormone and the gestational gland. J. Am. M. Ass. (Chicago), 84, 1715 (June 6).

Gley, E.: 1917. The internal secretions; their physiology and application to pathology. Hoeber, N. Y.

Hammett, F. S.: 1925. Inter-glandular associations. This Journal, 9, 297 (July-Aug.).

Hoskins, R. G.: 1925. Endocrine factors influencing bodily vigor. Proc. Ass. Study Internal Secretions, J. Am. M. Ass. (Chicago), 85, 298 (July 25).

Long, J. A., & Evans, H. M.: 1922. The oestrus cycle in the rat and its associated phenomena. Memoirs Univ. Calif. (Berkeley), 6, Univ. of Calif. Press.

Marine, David: 1923. Importance of our knowledge of physiology in control of thyroid diseases. Arch. Int. Med. (Chicago), 32, 811 (Dec.).

Stockard, C. R., & Papanicolaou, G. N.: 1917. Existence of a typical oestrus cycle in the guinea pig, with a study of its histological and physiological changes. Am. J. Anat. (Balt.), 22, 225 (Sept.).

Vincent, S.: 1925. Internal secretions and the ductless glands. Physicians & Surgeons Book Co., N. Y., p. 336.

Book Reviews

DIABETES: ITS TREATMENT BY INSULIN AND DIET. A HANDBOOK FOR THE PATIENT. Orlando H. Petty & Wm. H. Stoner, 1925. F. A. Davis Co., Phila. Pp. 133.

This diabetic primer includes chapters on the nature of diabetes; foods, salts and vitamines; measuring foods; methods of estimating diet; testing urine for glucose; insulin and its home administration; diatetic hygiene; recipes of a number of standard dishes with their food values; and selections from the Atwater Bulletin on composition of foods. The presentation seems to be somewhat too technical for the class of readers who would presumably find it most useful, but the fact that it is now appearing in a second edition indicates that it has found a useful place.—R. G. H.

CONTRIBUCION AL ESTUDIO DE LAS RELACIONES ENTRE LA HIPOFISIS Y LOS CENTROS DIENCEFALICOS. M. L. Sánchez, 1924. Univ. Nac. de Mexico, Fac. de Med., Mexico, D. F. Pp. 262.

As a doctorate thesis from the Mexican National University the author presents a study of the hypophysis and the related diencephalic centers. The first section reports a comparative anatomical investigation made in bathrachians, guinea pigs, rabbits, cats, cattle and man. This is followed by a section on histology and one on experimental results from extirpating the hypophysis and from injury of the tuber cinereum. Five clinical studies are then given in some detail of cases in which the hypophysis and diencephalic centers were affected. It is concluded that a functional relationship exists between these structures.—R. G. H.

PATHOLOGIE DU SYMPATHIQUE. Laignel-Lavastine, 1924. Librairie Felix Alcan, Paris.

The author has gathered into a volume of 1000 pages practically all that is known of the sympathetic system. The normal and the pathological anatomy is treated, first, of the sympathetic elements and then of the sympathetic system. This is followed by an exhaustive discussion of the physiology

and pathological physiology of the system. The third or clinical part is devoted to the syndromes classified in relation to the different systems of the organism: skin, muscles, bones, joints, circulatory, and nervous system, etc.

Of special interest are the original studies of the author on the solar plexus, his observations on the "tache blanche" and the classification of several hitherto unclassified diseases as belonging to the sympathetic field. It will not be amiss to remark, however, that, since what is known of illness is to a great extent reduced to sympathetic disturbances, there is hardly a disease which should not be regarded as at least partially "sympathetic."

In spite of the undeniable merit of the book one must realize that the long and diligent study on the pathological anatomy refers to lesions, that are anything but specific, hence it is hardly fair to call it "Pathological Anatomy of the Sympathetic." Similar comment might be made regarding the physiology, since our knowledge of the sympathetic centers is very little more than a blank. What we know is almost only a phenomenology of interrelation of which the determining points escape our observation.

All in all this is a valuable book, especially as a reference, that errs only in offering a perhaps premature systematization that may be misleading and by unjustified generalizations create new errors in the medical field. Should it be possible—to cite an instance—to demonstrate that the sympathetic is the nervous system of the mesodermic formations and, consequently, its role the maintenance of co-operation among the several organic systems, then perhaps its working could be understood. An elucidation might then follow of what we are still forced to call "functional" diseases, regarding only the symptoms which strike our eye, instead of looking for the "primum movens."

—G. V.

Abstract Department

Fixing of cholesterol in the nervous system in vitamin B deficiency (Die Bindung des Cholesterons im Nervensystem bei Mangel an Vitamin B). Verzár (F.), Kokas (Ester) & Arvay (A.), Arch. f. d. ges. Physiol. (Berl.), 1924- 206, 666-674.

In rats and pigeons on vitamin B deficient diets the cholesterol content of nerves decreases, and that of cholesterol esters increases to a greater extent. The changes are believed due to dysfunction of the adrenal cortex.—A. T. C.

Hypertrophy of the adrenal cortex with vitamin B deficiency (Die Hypertrophie der Nebennierenrinde bei Mangel an Vitamin B). Verzár (F.) & Péter (F.), Arch. f. d. ges. Physiol. (Berl.), 1924, 206, 659-565.

The cortex, and not the medulla, is affected. The ratio of medulla to cortex is in normal rats 1:9; in normal rabbits, 1:8. The corresponding ratios after vitamin deficiency are 1:14 and 1:12.

—A. T. C.

The influence of atropin upon the vascular response to Adrenalin (Über die Bedeutung der Atropinisierung für den Blutgefasseffekt des Adrenaline). Wehland (N.), Skandin. Arch. f. Physiol. (Leipz.), 1924, 45, 211-235.

Pithed frogs were used. Adrenalin following atropin gave vasodilation. A similar action of adrenalin followed after perfusion with a Ca-free solution. The author believes that atropin paralyzes the vasoconstrictor sympathetic nerve endings but does not influence the vasodilator sympathetic nerve endings.

—G. E. B.

The influence of diet on the action of certain internal secretions. V. (Studien über den Einfluss der Ernährung auf die Wirkung bestimmter Inkretstoffe. V.). Abderhalden (E.) & Wertheimer (E.), Arch. f. d. ges. Physiol. (Berl.), 1925, 207, 222-227.

Adrenin has a stronger action (as measured by the ensuing hyperglycemia) on rabbits fed an acid diet. Since this action is inhibited by ergotamine, it must depend on increased irritability of the sympathetic system, and the tonus of the sympathetic can therefore be influenced by diet. Ergotamine does not affect any change of reaction to insulin on different diets; the action of in-

sulin is independent of the sympathetic nervous system. Rats on carbohydrate poor or free diet, and rabbits on an acid diet, following glucose injection show more marked hyperglycemia than control animals on carbohydrate rich diet.—A. T. C.

Observations concerning obesity with report of cases of endogenous type. McKinlay (C. A.), Minnesota Med. (St. Paul), 1925, **8**, 354-358.

One case of endogenous obesity due to alteration of thyroid function is reported that illustrates a phase of the cycle variation of thyroid function occasionally observed. Another case of endogenous obesity with lowered basal metabolism is reported. This patient lost weight after the use of a low calorie diet and thyroid extract. In the obese, lack of weight loss after lowered food intake and sufficient exercise suggests a rational basis, under proper control, which includes estimation of the heat production of the body, for the addition of the use of thyroid extract. In a series of 33 cases of obesity, 28 classified as simple and 5 as pituitary in origin, the basal metabolism was normal in 23 cases, above 10% in 9, and below in 9. Signs of endocrine disease were found in 4 of the 9 patients with subnormal basal metabolism.

—Author's Abst.

Relation between vitamins and hormones. Scheer (K.), Ztschr. f. Kinderh. (Berl.), 1925, **39**, 166-173.

The administration of thyroid to young white rats which have been upon a vitamin free diet causes a prompt reduction in weight, and death is hastened. The symptoms of avitaminosis are also intensified. Testicular extract has a similar, though weaker, action. Thymus extract favors increase in weight and growth, and lengthens life, obviating in part the symptoms of avitaminosis. There is thus a direct connection between the growth vitamins and the thymus hormone —Physiol. Abst., **10**, 225.

Ovarian follicular hormone: distribution in human genital tissues. Allen (E.), Pratt (J. P.) & Doisy (E. A.), J. Am. M. Ass. (Chicago), 1925, **85**, 399-405.

A determination of the amount of active substance extracted from different human genital tissues is made by Allen, Pratt and Doisy. This is measured in rat units by means of a decisive anatomic and physiologic reaction of the genital tract of the spayed rat to injected lipoid extracts. The follicular hormone is present in greater concentration in large ovarian follicles of women than in those of pigs. In pigs and cows, the secretion of this hormone ceases or wanes rapidly following ovulation; in women, it is continued after ovulation by the corpus luteum for a considerable period. It seems possible that this may prove to be one of the prin-

cipal determining factors in the difference between the estrous cycle of lower mammals and the menstrual cycle of primates. Extracts have been made of placentas from women and cows which give the same growth reaction in test animals as does the ovarian follicular hormone. The human corpus of the first and third months of pregnancy contains some active substance, but the placenta contains much larger quantities. The evidence presented indicates that the corpus can be excised as early as 20 days following the last menstruation without interfering with normal gestation; consequently, this endocrine function of the corpus in woman during this time does not seem a necessary one. Two possibilities present themselves to explain placental endocrine function: either (1) the hormone extracted from the placenta is elaborated there, or (2) it is retained there after being formed in the ovarian follicles or (in woman) in the corpus luteum. Further experimental evidence is necessary to settle this point.—A. M. A.

Demonstration of the female sex hormone in the circulating blood. Frank (R. T.), Frank (Marie Louise), Gustavson (R. G) & Weyerts (W. W.), J. Am. M. Ass. (Chicago), 1925, **85**, 510.

The blood of five sows in estrus, five not in estrus, and the blood of one bull was collected. An alcohol benzene extract of each specimen was injected into one or more castrated rats, and the vaginal smear watched. None of the anestrous bloods, or the male blood, gave a positive reaction. Of the five bloods obtained from estrous animals, four gave positive results with a total dosage of 75 mg. of crude extract. With present methods of extraction at least 300 cc. of estrous blood is necessary to obtain 75 mg. of extract necessary for the test. Even with the present crude and not quantitative methods of concentration these results show that: (1) the female sex hormone can be recovered from the circulating blood, and (2) the quantity in circulation is greater during estrus than during the interval. It will be sought to devise quantitative methods of extraction which will permit the study of the amount of sex hormone present under physiologic conditions, such as prepuberty, puberty and the fertile and infertile sex cycle, as well as in pathologic states such as amenorrhea, sterility and menorrhagia.
—R. G. H.

Experimental hermaphroditism and the antagonism of the sex glands. I. Intrarenal ovarian transplantation. Indicators of feminine and masculine hormone effects in guinea pigs (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. I. Die intrarenale Ovarientransplantation. Die Indikatoren des weiblichen und männlichen hormonalen Effekts beim Meerschweinchen). Lipschütz (A.), Arch. f. d. ges. Physiol. (Berl.), 1925, **207**, 548-562.

A simple method of intrarenal ovarian transplantation is described which can be carried out extraperitoneally. It produces with male guinea pigs, castrated, or with·fragments of testes, almost always positive results, in some months, as judged by the feminine hormone effects of the condition of nipples and mammae.
—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. II. Hormone action and condition of testes-fragments in experimental hermaphroditism (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. II. Die hormonale Wirkung und das Verhalten von Hodenfragmenten bei experimentellem Hermaphroditismus). Lipschütz (A.) & v. Voss (H. E.), Arch. f. d. ges. Physiol. (Berl.), 1925, 207, 563-582.

In most cases where the testis-mass is reduced to a fragment ovarian intrarenal implantation produces maximum hormonal breast effects within 10 months, in the majority of cases milk being produced. The results, contrasted with those when ovaries are im-. planted without castration, indicate that the testes antagonize the feminine hormone. In many animals the masculine characteristics remained, and the testicular fragments frequently contained spermatozoa, indicating that the ovary does not definitely inhibit spermatogenesis.—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. III. The connection between the implanted ovarian mass and the latency time. Further observations on the conditions of the testicular fragments in experimental hermaphroditism (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. III. Ueber die Beziehungen zwischen der implantierten Ovarialmenge und der Latenzzeit. Weitere Beobachtungen über das Verhalten von Hodenfragmenten bei experimentellem Hermaphroditismus). Lipschütz (A.) & v. Voss (H. E.), Arch. f. d. ges. Physiol. (Berl.), 1925, 207, 583-595.

The latent period before the effects of the feminine hormone are observed after ovary implantation into partially castrated male guinea pigs varies with the mass of ovarian tissue implanted. The ovary of a 16-day-old female produces effects in a male after 2 or 3 weeks (hypertrophy of breasts), although in the original female these would not have been produced for 6 or 8 weeks. This may be due to an accelerated follicular development in the implant.
—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. IV. The antagonistic influence of the testis on the ovary. Sectional experiment (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. IV. Die an-

tagonistische Beeinflussung des Ovariums durch den Testikel. Der Entriegelungsversuch). Lipschütz (A.), v. Voss (H. E.) & Vesnjakov (S.), Arch. f. d. ges. Physiol. (Berl.), 1925, 208, 272-292.

In a male uncastrated guinea pig, in which intrarenal ovarian transplantation has not produced during some months any feminine hormone effect, removal of testes results in the production of this effect after a short interval. Presence of the testes inhibits the effect, probably delaying follicular ripening, and increasing the tendency to degeneration of the implant.—A. T. C.

Experimental hermaphroditism and the antagonism of the sex glands. V. The mechanics of action of the sectional experiment. Fractionation of the latency time (Experimenteller Hermaphroditismus und der Antagonismus der Geschlectsdrüsen. V. Ueber den Wirkungsmechanismus der Entriegelung. The Fractionierung der Latenzzeit). Lipschütz (A.), Lange (F.), Svikul (D.), Tiitso (M.) & Vesnjakov (S.), Arch. f. d. ges. Physiol. (Berl.), 1925, 208, 293-317.

The latency time can be divided into vascularization (of the transplant) time, ripening time, and reaction time. Transplantation of a rabbit ovary into a castrated guinea pig never produces the feminine hormone action.—A. T. C.

Ovarian grafts. Experimental and clinical results as regards menstruation, fecundation and pregnancy (Greffes d'ovaires Résultats expérimentaux et cliniques concernant la menstruation, la fécondation et la grossesse). Tuffier (T.) & Bour (D.), Presse méd. (Par.), 1925, 33, 1073-1076.

From a somewhat extensive review of the experimental and clinical literature and personal experience in 50 clinical cases Tuffier and Bour conclude that free ovarian grafts implanted during the genital life of the woman, and especially autografts, give very good results as regards the general health. Menstruation is reestablished usually in 3 to 5 months after the operation and persists at least 5 to 6 years. Experiences in animals and in women have proved that after this operation pregnancy can occur. Transplantation in the uterus of an ovary supplied with its vascular and nervous peduncle is a beneficial operation in well determined cases. The vascular peduncle being unharmed, the ovary is perfectly nourished, and the follicles arrive at maturity and can discharge ova into the uterine cavity. Fertilization is possible and pregnancy can often go to term, and healthy offspring be born. In every case; transplantation is beneficial since the ovary lives and functions afterwards, menstruation is not often disturbed in periodicity nor in duration, and since the woman, in a condition of general

GONADS

good health, escapes the symptoms of early menopause. The only inconvenience arising from the transplantations, as in all partial operations on the utero-ovarian organs of women, is that in 50% of the cases there are slight pains before menstruation.

—R. G. H.

Activity studies on male castrated rats with ovarian transplants, and correlation of the activity with the histology of the grafts. Wang (G. H.), Richter (C. P.) & Guttmacher (A. F.), Am. J. Physiol. (Balt.), 1925, 73, 581-599.

The basis for these experiments was the observation that the running activity of males castrated at an early age always remains on a low level, and that there are sex differences in activity which can be measured; the four-day cycle present in the female and absent in the male, and the higher running level of the female. Transplantation of ovaries into castrated males may produce a marked increase in activity. The amount of the increase in 17 out of 24 animals varied from 1.03 to 116 times the pretransplantation level. The remaining 7 animals showed a decrease in activity after the operation. Five of the castrated males after ovaries had been transplanted into them ran as much as normal females and considerably more than the average male. Four others reached the average for males, while the rest ran less than either males or females. In 4 of the animals the activity cycles characteristic of the mature female rat were produced, but were not quite so regular as they are in normal females. Very much less regular activity cycles were present in 9 other animals. The remaining animals showed no cycles at all. Twelve of the animals showed a change in body weight following transplantation, that is, the more rapid rate of growth of the castrated males was diminished until the body weight curve closely approximated the body weight curve of the normal female. When the grafts were removed the body weight increased again to the male level. Five animals showed small and somewhat doubtful changes in body weight, while 7 showed no changes at all in body weight. Histological examination of the grafts showed that ovarian tissue was present in all animals with either a change in activity or body weight. The grafts contained graafian follicles, ova, and corpora lutea, but they did not present the histological picture of completely normal ovaries. The grades of activity and body weight changes were not correlated with definite histological differences in the grafts, except that in animals which showed neither an increase in activity nor a body weight change the grafts were completely absorbed. Because of the absence of any correlation between the activity changes and the histology of the grafts an attempt was made to determine whether the weight and activity changes might not be correlated with the histological picture on the basis of different degrees of vascularization

of the grafts.   However, no such correlation could be established.
<div align="right">—Authors' Summary.</div>

The ovarian hormone.   Zondek (B.) & Aschheim (S.), Klin.
. Wchnschr. (Berl.), 1925, 4, 1388-1390.

The cytology of the vaginal secretion in the white mouse is
closely dependent on the physiologic cycle of the ovary, as is also
the hormone action of implanted material in the castrated animal.
Zondek and Aschheim examined on this basis the action of dif-
ferent organs on the sexual cycle.   Glandular and endocrine organs
did not influence the sexual periods.   Ovarian substance provoked
the cycle in a few days.   Only the wall of mature or nearly mature
follicles or their liquid content is active.   The only other organ
which contains the active prnciple is the placenta.
<div align="right">—J. Am. M. Ass., 85, 710.</div>

The content of posterior pituitary secretion present in cerebrospinal
fluid (Ueber den Gehalt der Cerebrospinalflüssigeit an Hypo-
physenhinterlappensekret).   Miura (Yoshio), Arch. f. d. ges.
Physiol. (Berl.), 1925, 207, 76-84.

Experiments with cats show that the cerebrospinal fluid from
the fourth ventricle contains a slight amount of the uterus-stimu-
lating substance of the posterior pituitary.   After removal of the
pituitary the fluid ceases to possess this property.—A. T. C.

Medical treatment of pituitary neoplasm.   Pardee (I. H.), J. Am.
M. Ass. (Chicago), 1925, 85, 513-515.

A brief review of the literature and four illustrative case re-
ports are offered.   The gradually increasing number of case reports
in the literature and the experience of those working in the au-
thor's clinic are taken to indicate that all pituitary neoplasms,
whether large or merely hyperplasias, should be given the benefit
of medical treatment, provided vision is not in immediate danger
of becoming lost.   First, glandular extracts should be used, especi-
ally pituitary and pituitary extract, and, as a later resort, roent-
gen-ray treatment.   Many patients under this procedure will be
saved from a major operation, the outcome of which is often prob-
lematic.   The types of cases most likely to respond to the fore-
going method are those of pituitary hyperplasia and adenoma,
which are not of the destructive type and do not seem to be grow-
ing rapidly.   These often show symptoms of glandular disturbances
elsewhere and will often develop erosion and enlargement of the
sella, chiasmal pressure and, perhaps, signs of pyramidal tract
pressure.   The glandular therapy recommended is desiccated pitui-
tary body by mouth and pituitary extract hypodermically.   Com-
bined with this, any necessary supportive or substitutive therapy
should be given to other endocrine organs.   Many patients recov-
ered under the foregoing treatment.—R. G. H.

The effect of pituitary extract on the secretion and composition of the urine. Stehle (R. L.) & Bourne (W.), J. Physiol. (Lond.), 1925, 60, 229-236.

Studied effect of pituitrin in normal fasting dogs with bladder fistulas. When the initial urine flow was high an antidiuretic effect was produced smilar to that in diabetes insipidus. With low initial flow diuresis resulted. The most striking results were obtained in chloride excretion which was increased as much as 74 times (minute rate). This effect was mostly suppressed when the dogs were anesthetized. The authors regard their results as most likely due to local effects in the kidneys rather than on body metabolism. Phosphate and urea excretion were also augmented but to a lesser degree than chloride.—R. G. H.

A case of dyspituitarism following encephalitis lethargica. Worster-Drought (C.), Brain (Lond.), 1925, 48, 127-128.

A boy aged 14 developed encephalitis. Since convalescence he has gradually developed the picture now presented of general adiposity, normal genitalia, relative lymphocytosis, increased sugar tolerance, and a blood sugar curve suggesting dyspituitarism of the Dercum type. It is possible that the condition is due to involvment by encephalitic process of the nuclei of the tuber cinereum, rather than of the pituitary.—A. T. C.

The control of blood pressure with liver extracts. James (A. A.) & Laughton (N. B.), Canad. M. Ass. J. (Montreal), 1925, 15, 701.

Protein-free extracts of liver effectually reduce the hypertension effects of adrenin, pituitrin, isoamylamine, and parahyroxyphenylethylamine in rabbits, and reduce their normal blood pressure to about 50 mm. of mercury for prolonged periods. With large doses death ensues. It is believed that the active substance is not choline or histamine.—A. T. C.

Extractives of liver possessing blood pressure reducing properties. Macdonald (W. J.), Canad. M. Ass. J. (Montreal), 1925 15, 697-701.

Extracts of liver, stated not to be of protein nature, but of which the method of preparation is not given, when injected into normal rabbits produced marked falls of blood pressure. In a number of cases of marked hypertension the majority showed definite fall in blood pressure, lasting after a single injection for from one to three days.—A. T. C.

Action of insulin (Beitrag zur Kenntnis der Wirkungen des Insulins). Abderhalden (E.) & Gellhorn (E.), Arch. f. d. ges. Physiol. (Berl.), 1925, 208, 135-145.

Experiments on intestine and uterus of mammals show that commercial insulin preparations produce a paralyzing action on tone and automaticity of the intestine, due to their phenol content. Phenol-free preparations produce a characteristic increase of tonicity. Choline and adrenin action is strengthened. Acetylization of insulin preparations show that they contain slight amounts of choline. The authors believe that the apparent antagonism between insulin and adrenin is traceable to this choline content.

—A. T. C.

Trophic action of insulin. Ambard (L.) & Schmid (F.), Bull. Soc. méd. d. hôp. (Par.), 1925, **49**, 904.

Ambard and Schmid describe a case in a woman, aged 67, with an apparently tuberculous skin lesion on one foot, which developed into a deep and large ulcer (20 by 20 cm.) of the infectious type. As various measures used during 5 months did not prove successful, wet dressings with insulin were tried (12 units twice a day). No changes were noted the first 12 days; then granulations appeared, followed by complete healing in about 10 days. In other cases small ulcers healed in a week, after other measures had failed. In only one case out of 14 did insulin fail to give results. In the beginning the insulin was given subcutaneously, afterward the wound was powdered with it. The action is ascribed to an exaggerated cellular activity of the tissues resulting from stimulation of the carbohydrate metabolism.

—J. Am. M. Ass., **85**, 473.

Insulin in treatment of ulcers. Chabanier (H.), Lumière & Lebert, Bull. Acad. de méd. (Par.), 1925, **94**, 782-784.

Chabanier, Lumière and Lebert treated with insulin 10 nondiabetic patients with varicose ulcers. Two daily injections of 40 units each were given and dressings with insulin ointment were applied locally. Neither special diet nor rest were prescribed. In one of the patients, aged 61, with two ulcers of 20 years' standing, under the general and local insulin treatment, one ulcer healed in 19 days, the other in 30 days. Another patient, aged 51, with recurrent ulcer of the leg the last 10 years, was cured in 10 days, the ulcer being completely healed. In a diabetic girl treated during the last 2 years with large doses of insulin (80 units daily) an ulcer had developed on each sole in the last 3 months. Applications of insulin ointment were followed by total healing of the ulcers in less than a month.—J. Am. M. Ass., **85**, 706.

Changes in the physiological action of insulin induced by exposure to ultraviolet light. Ellis (M. M.) & Newton (E. B.), Am. J. Physiol. (Balt.), 1925, **73**, 530-538.

Insulin solutions exposed in an atmosphere of nitrogen in

transparent fused-quartz tubes to the action of the ultraviolet light from a mercury vapor lamp for periods of from 19 to 48 hours lost their power to produce hypoglycemia when injected into test animals. Some substance or substances were developed in these exposed insulin solutions which produced hyperglycemia when injected. Insulin solutions under nitrogen in pyrex glass test tubes which filter out most of the short rays did not lose their power to produce hypoglycemia when injected into test animals, after 48 hours' exposure under the mercury vapor lamp, although quantitatively the 48-hour samples seemed slightly less potent than the unexposed controls. These changes in the insulin solutions were not due to the presence of tricresol. Ozone and free oxygen in ordinary daylight destroyed the power of unexposed insulin solutions to produce hypoglycemia, but did not develop hyperglycemia-producing substances in one-hour treatments. A possible "activating" action of ultraviolet light on insulin in nondestructive exposures is mentioned.

—Authors' Summary.

Insulin treatment of leg ulcers. Faure-Beaulieu & David, Bull. Soc. méd. d. hôp. (Par.), 1925, 49, 892-895.

Ten of Faure-Beaulieu and David's patients with leg ulcers presented hyperglycemia, while no sugar was detected in the urine. They were treated with insulin in dosage of 10 units subcutaneously twice a day. In one case the total amount of insulin was 1,600 units; usually, about 500 units. One woman with an ulcer 11 by 7 cm. in size and glycemia of 0.212 gm. per 100 cc. was cured in 2 months. She was given 480 units of insulin. A similar ulcer the year before took 7 months to heal. Another woman with an ulcer 7 by 9 cm. and glycemia of 0.241 gm. was completely cured in one month (320 units). One syphilitic woman had had a large and very painful ulcer for 4 years, rebellious to specific treatment. After 2 months' injections of insulin the ulcer, 14 by 10 cm., was reduced by a half. The glycemia in this woman was 0.216 gm.

—J. Am. Ass., 85, 473.

Observations upon the action of insulin on the blood, with special reference to the cause of the condition known as hypoglycemia. Foshay (L.), Am. J. Physiol. (Balt.), 1925, 73, 470-479.

It has been shown that insulin causes a reduction in the quantity of glucose in the dog's erythrocytes disproportionate to the reduction in the whole blood, and that it causes the same response in human blood. Moreover, it has been shown that insulin reactions can occur without hypoglycemia, both in man and in the dog, and that such reactions in the dog begin simultaneously with the reduction of the corpuscular glucose. This offers a probable explanation of the failures to find the blood sugar low in the majority of the cases of insulin reactions, for only the whole blood sugar was

measured. The train of symptoms and signs that follows administration of large doses of insulin, and at least the early subjective and objective phenomena of insulin overdosage, are not associated with a hypoglycemia per se, but rather with a cytoglycopenia—a status of glucose impoverishment within the cell. This is of importance in the treatment of diabetes, especially when large doses of insulin are used. For, as has been shown, the whole blood sugar determination, which is commonly used as the therapeutic guide, is not a reliable index of an approaching insulin overdosage. This is particularly true of a patient in coma, when the symptoms are absent and the signs are obscured, for then another large dose of insulin, given because the last whole blood sugar was still quite high, may lead to a fatal issue. Corpuscular sugar determinations are a reliable index of the physiological activity of insulin. They give evidence of degrees of action which are not obtained from whole blood sugar measurements.—Author's Summary.

Therapeutic uses of insulin in oily emulsion (Essais thérapeutiques avec l'insuline en émulsion huileuse). Hedvall (E.), Acta med. Scand. (Stockholm), 1925, 62, 334-350.

Hedvall sought to develop a practical method of rendering less irksome the administration of insulin. A careful clinical study showed that an oily emulsion, injected intramuscularly or subcutaneously, is resorbed more slowly than insulin otherwise administered and its action persists longer. The resorption is not slow enough in case of intramuscular injection to permit only one injection daily. In many patients, however, a single injection of the insulin emulsion subcutaneously can take the place of two or more injections administered in the usual way. But with larger doses hypoglycemia may follow if there is only one injection a day, and the danger is too great to render the method of any practical advantage.—R. G. H.

The growth, development and prognosis of diabetic children. Joslin (E. P.), Root (H. F.), & White (Priscilla), J. Am. M. Ass. (Chicago), 1925, 85, 420-422.

Joslin, Root and White have investigated this problem by studying the histories of 302 bona fide diabetic children. Of these, 162 died and 132 are alive. If a diabetic child gained weight before the discovery of insulin, it was considered an extraordinary event. When it did occur it was temoprary, and the weight quickly fell to below that at onset. The weight of the diabetic child treated with insulin increases. The increase in weight of 34 diabetic children treated with insulin over an average period of 18 months exceeds that of the normal child for the same length of time. An increase in height is present in the insulin-treated diabetic child, but it is distinctly less than that of the normal child. Unaided by insulin, no

girl in the series developed menstruation after the onset of diabetes. Since the use of insulin, 4 girls have begun to menstruate for the first time, and in another the onset of menstruation and diabetes were simultaneous. Menstruation ceased in 6 patients without insulin treatment, or became irregular soon after the onset of diabetes. The appearance of the boys has so changed that there is little doubt of their having matured. Of the 164 children treated without insulin, there remain but 12 alive. The 152 patients who died survived 2.4 years, and that constitutes the prognosis of the noninsulin-treated diabetic child. Of 130 children treated with insulin 120 are living.—A. M. A.

The liver in insulin hypoglycemia (Il fegato nella ipoglicemia da insulina). Villa (L.), Boll. soc. med.-chir. di Pavia, 1925, 37, 105-115.

Insulin hypoglycemia is due to an action taking place chiefly in the liver, but in a smaller degree also in muscles; this action consists of the inhibition of glycolysis. Adrenalin stops the inhibitory action of insulin and restarts the glycolytic function of the liver; it is, therefore, a more rational antidote than glucose itself.
—Physiol. Abst., 10, 229.

Treatment of sprue by parathyroid extract. Field (C. P.), J. Roy. Army Med. Corps (Lond.), 1925, 44, 456-457.

Successful treatment is recorded in a (pregnant) subject, with 0.1 gr. parathyroid extract twice a day, calcium lactate, 30 gr. daily, and a daily bowel wash of saline.—A. T. C.

The influence of Liebig's extract in experimental tetany (Ueber den Einfluss von Liebig's Extrakt auf die experimentelle Tetanie). Sinelnikoff (E. I.), Arch. f. d. ges. Physiol. (Berl.), 1925, 207, 351-360.

Flesh feeding has no harmful influence on thyroidectomized dogs with undamaged parathyroids, while raw meat leads to and increases all the tetany symptoms in parathyroidectomized dogs. The actual poison of raw meat passes into the watery extract, and long cooked meat has no noticeable poisonous action. Liebig's extract in a dose of 4 to 5 gms. per kilo body-weight produces in parathyroidectomized dogs all the symptoms of tetany within 0.5 to 2 hours after introduction into the stomach. Raw flesh, broth, and Liebig's extract contain guanidine and methylguanidine. Guanidine in doses corresponding to the amount present in flesh extracts does not completely produce tetany, and is less active than Liebig's extract and raw flesh. The poisonous action of Liebig's extract is probably due to the combined action of methyl-guanidine, carnitine, oblitine, etc. The liver, as well as the parathyroids, exercises a definite protective function against guanidine.—A. T. C.

The after effects of thyroid extirpation (Beitrag zur Kenntnis der Folgen der Schilddrüsenexstirpation). Abderhalden (E.), Arch. f. d. ges. Physiol. (Berl.), 1925, **208**, 476-486.

Experiments in guinea pigs show that there are marked differences in different individuals following thyroid extirpation.—A. T. C.

Tryptophan and thyroid function. Abel (A. R.), Backus (R. W.), Bourquin (H.) & Gerard (R. W.), Am. J. Physiol. (Balt.), 1925, **73**, 287-295.

White rats were fed on diets similar except for their content of tryptophan, thyroxin, and protein. The variations in the diets were: (1) protein as casein largely or entirely; (2) as zein and gelatin with the addition of tryptophan; (3) as zein and gelatin with no added tryptophan or thyroxin; (4) as zein and gelatin with the addition of thyroxin. Rats on the tryptophan-free diet developed characteristic symptoms leading to death. The thyroid gland showed a slightly increased cellularity. Minute amounts of tryptophan in the diet did not alter the symptoms but prevented any change in the thyroid. The symptoms once developed were not relieved by later adding tryptophan or thyroxin to the diet though tryroxin transformed some of the glands to the colloid state with evidences of atrophy. Thyroxin added to the tryptophan-free diet from the start rendered the thyroid colloid and very atrophic and prevented entirely the tryptophan-free symptoms, except emaciation and death. These facts indicate that: tryptophan is essential to the normal functioning of the thyroid; a large amount of the needed tryptophan is available for the thyroid from the tissues of the body; the thyroid is able to take up tryptophan from the blood in quantities approximating its needs, even when the total amount is so small that other tissues suffer from its lack; sufficient thyroxin from an outside source induces atrophy of the thyroid. Lack of tryptophan results also in extrathyroid disturbances leading to emaciation and death.—Authors' Summary.

Two cases of adolescent myxoedema accompanied by nephrosis, and in one case, tetany. Davidson (J. R.), Canad. M. Ass. J. (Montreal), 1925, **15**, 598-600.

A case of adolescent myxoedema, accompanied by nephrosis and by tetany of parathyroid origin, treated with thyroid and Collip's parathyroid extract. Davidson (J. R.), Canad. M. Ass. J. (Montreal), 1925, **15**, 803-808.

Thyroid treatment in the first case brought the basal metabolic rate to normal, and apparently decreased the nephrosis.

Thyroid and calcium treatment of the second subject caused the symptoms of myxoedema almost to disappear, while the tetany

convulsions markedly diminished in number and severity. Combined thyroid (by mouth) and Collip's parathyroid extract (subcutaneous injection) over a period of 6 months kept the basal metabolic rate within normal limits, and the serum calcium between 10 and 11.5 mg. per 100 cc. There was gradual improvement and almost complete elimination of convulsions in spite of many intercurrent infections to which the patient was extremely susceptible, and one of which ultimately proved fatal. The diagnosis was confirmed at postmortem.—A. T. C.

Iodin hyperthyroidism. Jackson (A. S.), Am. J. M. Sc. (Phila.), 1925, **170**, 271-283.

The number of cases of iodin hyperthyroidism has greatly increased, due to the popular demand for iodin in the treatment of goiter. In the series of 38 cases reported in this article 20 were observed within the past six months. Two cases terminated fatally. This condition had generally been termed iodin-Basedow in the literature, and consequently has been confused with exophthalmic goiter. Iodin should not be distributed promiscuously either in water or salt, but should be administered in exact amounts and under a physician's order. Even minute amounts of iodin are sufficient to initiate symptoms of hyperthyroidism in certain persons with adenomatous goiters. Iodin should be administered with particular care to children with adenomatous goiters; it should never be given to adults with this condition. Every child in the goiter belt between the ages of 10 and 20 years should receive small weekly doses of iodin for the prevention or treatment of colloid goiter. Iodin hyperthyroidism is rare in persons under 30 years age. It develops only in the presence of an adenomatous goiter. The clinical syndrome may be clearly distinguished from that seen in toxic adenoma or exophthalmic goiter. Thrills, bruits and exophthalmos do not occur. If an early diagnosis is made medical treatment may abort the toxic symptoms. Thyroidectomy is indicated when the condition does not yield to medical measures. The pathological picture is not characteristic. Grossly, the gland has the typical appearance of an adenomatous goiter containing degenerated, cystic, fibrous and calcareous encapsulated nodules. Colloid may be seen in large amounts. The microscopical picture shows acini of variable size, lined with flat, cuboid cells, and filled with colloid. Fetal acini and occasional small areas of hypertrophic cells are found.—Author's Summary.

The physiological properties of substances from the isolated thyroid (Ueber die physiologischen Eigenschaften der Substanzen der isolierten Schilddrüse). Maloff (G. A.), Arch. f. d. ges. Physiol. (Berl.), 1925, **208**, 335-342.

Locke's solution, perfused through the isolated thyroid, con-

tains substances which increase the irritability of the sympathetic nerve endings, and thereby increase the sensitivity of the (isolated) liver vessels to adrenin, but have no effect on the isolated heart, the vessels of the isolated extremities, or the frog liver.—A. T. C.

The thyroid and the nervous system. Oswald (A.), Klin Wchnschr. (Berl.), 1925, 4, 1053-1055.

Oswald attributes to the instability of the nervous system the degree of sensitiveness to administration of thyroid extracts. Tachycardia, nervousness, tremor or sweating has been produced by thyroid extracts experimentally only in fox terriers degenerated from inbreeding. He found that thyroid extract increases the action of pilocarpin, histamin and morphin. The bradycardia following an injection of pilocarpin is more pronounced and lasts longer under the influence of thyroid extracts. They sensitize the nervous system and the latter increases the action of the thyroid gland, which thus serves as an amplifier of the impulses. Thyroxin is not the full hormone because it does not act on the nerves regulating the blood circulation and on Auerbach's plexus. It is an artificial split product. Only the thyroglobulin is, in the author's opinion, the true hormone of the thyroid.—J. Am. M. Ass., 85, 396.

Relation between experimental tuberculosis and the thyroparathyroid system (Rapporti fra tubercolosi sperimentale e sistema tiroparatiroideo). Salvioli (G.), Boll. Ist. Sieroter. (Milano), 1924, 3, 197-240.

The dog is a useful experimental animal in the study of tuberculosis. After parathyroidectomy dogs are more resistant and after thyroidectomy more sensitive to the disease. If over-regeneration of the thyroid occurs, however, the infection is impeded. The author believes that thyroid treatment may be helpful.—P. M. N.

Studies on mitochondria. I. The changes occurring during experimental thyroid hyperplasia and its involution with iodine. Secoff (D. P.), Am. J. Pathol. (Bost.), 1925, 1, 295-303.

Secoff has studied the mitochondrial variations during the developmental stages of hyperplasia induced in the thyroids of cats, rats, rabbits, guinea pigs, pigeons and chickens by high fat diets, and during compensatory hypertrophy in the guinea pig, as well as those occurring during the involuntary response produced by iodine. This report is concerned with his observations on the rat and guinea pig, although they were the same in all the animals studied. The number, morphology and distribution of the mitochondria in the thyroid cell vary directly with the degree of active hyperplasia or involution. During the developmental stages of active hyperplasia

ception of the morphology and function of the thyroid, known patho-
logical entities in this gland are referred to their point of departure
from the normally functioning organ. "Hyperthyroidism" is dys-
thyroidism with a definite histological basis. Graves' disease is of
two types: primary, associated with adenoid goiter; and secondary,
with primary arterio-capillary sclerosis of the gland; in both forms
it is something more than a simple dysthyroidism. Vesicular goiter
is a distinct entity, is the histological obverse of adenoid goiter, and
is probably a true hypothyroidism. "Adeno-parenchymatous" goiter
is distinct from vesicular goiter, though the two types together con-
stitute the class termed endemic goiter. Under hyperplastic goiter
two states are defined—one referable to an anatomical deficiency,
the simple type; and the other to a physiological deficiency, the
lymphadenoid type. Myxoedema has a characteristic histopathology
and is not a mere incidental atrophy of the thyroid gland.—J. P. S.

THERMOGENESIS AS THE FUNDAMENTAL FUNCTION OF THE ADRENAL MEDULLA AND CORTEX*

CHARLES E. DE M. SAJOUS, M.D., Sc.D., LL.D.
Professor of Endocrinology, University of Pennsylvania Graduate School of Medicine

PHILADELPHIA

Despite the brilliant researches of chemists, physicists and physiologists, initiated by the labors of Lavoisier and Laplace in 1780, the most important fundamental problem of medical science, tissue respiration, is still admittedly unsolved. Indeed, the casual remark of an editorial writer (1) in the Journal of the American Medical Association, in 1919, that "an answer to the question as to how the all-important oxidations in the body are brought about is almost as obscure to-day as it was a hundred years ago" tallies well with Howell's declaration in 1924 (2), that "the respiratory history of oxygen ceases after this element reaches the tissues." The deplorable feature entailed is the widespread obscurity that it perpetuates in medicine as a whole. This is well emphasized by Halliburton's (3) statement in 1921, that "knowledge of tissue respiration is so scanty that we can say but little of its pathological bearing." That a question exercising such deep influence on medical progress should so long have resisted the painstaking efforts of hundreds of investigators of the first order seems pointedly to suggest that some basic

---

factor has been missing all along to deprive their labors of fruit-ful results.

Over two decades ago, and repeatedly since, I submitted that this missing factor is the secretion of the adrenals. My purpose to-day is to draw your attention to the fact that this interpreta-tion has, in recent years, been confirmed independently by many physiologists, pharmacologists and clinicians, while, on the other hand, those investigators who have overlooked the connection between the respiratory process and the adrenals have been un-able to indicate any fundamental function for these organs.

Having published much of this evidence in *Endocrinology* and elsewhere (4), I shall only present in the present paper a sufficient summary of the functional connection between the med-ullary secretion, the respiratory process and general metabo-lism, and submit that the adrenal cortex also participates in the latter process in conjunction with the medullary secretion.

The diffusion doctrine of respiration, I may recall, has been assailed ever since 1856, when various prominent physiologists, Paul Bert, Müller and Zuntz and others, urged that when the access of air to the lungs, in strangulation, for instance, was prevented, the pulmonary blood continued to exhaust the alveo-lar air of all its oxygen. Several expeditions to high altitudes, i. e., to highly rarefied air, Pike's Peak, Mt. Everest, etc., have sustained these observations. Again, various British physiolo-gists, Vaughn, Lorrain Smith and Haldane (5), and particu-larly Prof. Bohr (6), of Copenhagen in 1891, have urged, in order to explain the phenomena witnessed and aerotonometric divergences, the need of some substance in the blood which could take up and clutch the oxygen from alveolar air. They all failed, however, to identify this substance.

In 1903 (7) I submitted that the substances sought by Bohr and his school was the secretion of the adrenals; that it took up the oxygen from the pulmonary air, caused expulsion of carbon dioxide, and that it sustained respiration. Among the facts which had led me to this conclusion were tests which emphasized the marked reducing properties of adrenal extractives and, after 1901, of adrenalin, and also their influence on temperature, their activity as oxidases, the obvious course of the adrenal

secretion towards the lungs, and also what biochemical and clinical data the literature and the clinic afforded at the time.

For a number of years, due mainly to the confidence which the tonus theory of Oliver and Schäfer had inspired, my views were neglected. When, however, the tonus theory was apparently controverted by physiologists, the strength of my own position began to assert itself. Thus, numerous investigators (enumerated in the grouped bibliographical list appended to this paper) (8), found independently that adrenalin increased the intake of oxygen, the output of carbon dioxide and the volume of air breathed, and that it was secreted by the adrenals in quantities sufficient to produce these phenomena and also to raise the temperature and respiratory quotient.

My contentions that it was the corpuscular hemoglobin which took up the adrenal product and that it became on exposure to the alveolar air, oxyhemoglobin, were likewise confirmed. It was found that adrenalin could itself act as hemoglobin (9); that it increased the reducing power of hemoglobin while passing through the lungs; that venous blood from the adrenal veins, when diluted with salt solution, became red and showed spectroscopically increased formation of hemoglobin, while adrenalin added to ordinary venous blood was found to do likewise (10, 11).

Further indicating an intimate connection with the respiratory process were the observations that adrenalin caused dilatation of the bronchioles irrespective of any rise of blood pressure, thus facilitating the entrance of air into the alveoli (12, 13), and that one-tenth of a milligram of adrenalin proved sufficient to increase the respiratory excursions of the lungs (14).

I had also submitted (15) that the adrenal product I had termed "adrenoxin" became after exposure to the alveolar air, a catalytic oxidase I termed "adrenoxidase," which sustained tissue respiration and metabolism. Recently, R. G. Hoskins (16) also referred to adrenalin as a "respiratory catalyst," while Halliburton (17) recalled that blood pigments, such as hemoglobin, partake of the nature of ferments which have a catalytic action.

The personal view, that adrenoxidase carried on general metabolism, in so far as the part played by oxygen therein was

concerned, has also been sustained (18). Adrenalin was found in the red corpuscles and in the blood (19, 20), and the activity of the latter as an oxidase and catalase was found to correspond with its content in red corpuscles (21). Adrenalin was also found in the tissues and shown to accelerate basal metabolism after raising the respiratory quotient (22), while adrenal tumors (23) and grafts (24) were found to raise the temperature to a dangerous level irrespective of any infection. In doses within the quantities secreted by the adrenals, adrenalin proved itself capable of increasing both heat production (25) and the excretion of urea (26).

I had repeatedly, beginning with 1903, attributed to an excess of adrenal secretion, the production of fever (27). A similar connection was recently vouchsafed by Cannon and Pereira (28). The fact that adrenalin materially increases the metabolic activity of the the skeletal muscle was recently confirmed by Hoskins and Durrant (29). Hoskins and Hunter (30) also found that a suitable solution (1:100,000,000) of adrenalin caused active reaction of intestinal segments. The clinical importance of this rôle has been repeatedly emphasized. In 1903 (31) I urged that the serous diarrhea of Asiatic cholera was due to advanced failure of the adrenals. Naame and others have since found in Tunis and during the Balkan War that large doses of adrenalin were very efficient in this disease. In a personal case of serous diarrhea in which a bowel movement occurred every half-hour, treatment in all great European centers (the patient residing in London), for twenty-seven years had proven futile. Five weeks' use of adrenalin arrested the disorder, and the accompanying adynamia, hypothermia, etc. The brain was also found by Caskey and Spencer (32) to be influenced in the same manner by adrenalin, the amplitude of the temperature change and the changes in the blood pressure being proportionate to the amount of adrenalin used, provided the latter did not exceed a certain limit.

All these phenomena have been attributed by some authors to mere pharmacological effects, but the fact that the obliteration of adrenal functions provokes opposite effects indicates that such is not the case. The symptoms of Addison's disease, due to destruction of the adrenals, removal of these organs, pressure

on their nerves or vascular supply clearly emphasize this fact. These include, for example, when sufficient time is allowed for the drainage of accessory adrenals, steady decline of the temperature, prostration, respiratory inhibition, air hunger, lowered output of CO_2 and of O intake, decreased heat production, slowed basal metabolism (33) and decreased excretion of urea (34).

When, as is now the case, experimental demonstration is accepted as the sole arbiter, over sixty of such demonstrations, all pointing in the same direction such as the above summary represents, speak for themselves. Particularly is this the case when, as basis of comparison, we realize that the labor of physiologists who have overlooked this connection have yielded either nothing tangible or incidental effects which can all be traced back to the fundamental function of the adrenals on tissue respiration and metabolism. The tonus theory of Oliver and Schäfer which I deem sustained when the functions I attribute to the adrenal cortex are taken into account, and the emergency theory of Cannon, I regard as such incidental manifestations of this fundamental function.

Reduced to its simplest expression, the role of the medullary portion of the adrenals in the respiratory process, pulmonary and cellular, as I understand it, is to secrete *adrenoxin*, a reducing proferment, which, on reaching the pulmonary alveoli, takes up oxygen from the air and becomes, through this process, the oxidizing enzyme *adrenoxidase*. As such and as a component of the corpuscular hemoglobin, it converts the latter into *oxyhemoglobin* and takes part as such in general metabolism. Though itself a catalytic, as are all enzymes, adrenoxidase acquires, owing to the presence of iron and manganese in the hemoglobin, still greater catalytic activity.

What are the functions of the adrenal cortex, which constitutes nine-tenths of the whole gland?

Practically all investigators are in accord that the adrenal cortex is an important structure, judging from the fatal effects of its removal unless amply supplemented by accessory organs, as in the rat, its influence on body growth and on the development of the secondary sex characters, the lesions it shows in various infections, after burns, etc. But, again do we encounter

dense obscurity when we attempt to learn how any of these phenomena are brought about. Thus, it is well known that the three cortical zones, the glomerular, fasciculate and reticular, contain lipoids: lecithin rich in phosphorus (3.88 per cent.) as first shown by Bernard and Bigart in 1902, and Mulon in 1903, and of cholesterol, a monatomic alcohol, containing no phosphorus. The presence of these lipoids in the adrenal cortex has been verified by many observers. As to the role of these substances in the tissues, we also learn, however, from a leading authority, Hugh MacLean (35) that "the special part played by the lipoids in the organism is entirely unknown."

While it would appear that we are dealing with a very complex problem, the fact remains that when the role of the medullary adrenal product is recognized as the dominant factor of tissue respiration a flood of light facilitates the study of the lipoids and their functions in the body at large. We shall now briefly consider in logical sequence the various phases of lipoid function which appear to me elucidated.

The first of these is that both lecithin and cholesterol are, like oxygen, found in all tissues. Thus, as stated by Linossier (36) one of France's best biochemists, "the lipoids form part of all living substance"; cytologists specify that lecithin and cholesterol are ubiquitous constituents of protoplasm. This applies as well to nervous tissue. Two decades ago (37), I wrote a 100-page histological study of the neuron in which I submitted that in the presence of the adrenal oxidizing enzyme (adrenoxidase) in the axis cylinders and fibrils we were afforded not only an explanation of the circulation in the nerve cell (a field to which Harvey could not extend his epochal investigations, histology being unknown in his time), but also of the metabolism in the nerve cell as regards thermogenesis therein.

Is the lecithin-cholesterol-adrenoxidase triad not also concerned with general tissue respiration and metabolism?

As to the lecithin, such a connection has long been noticed but has remained unexplained. Howell (1924) states (38), for example, that "it evidently plays some as yet unknown part in cell metabolism." That it does this by provoking thermogenesis is indicated by many facts. As shown by Miescher in 1866 and other biochemists since, those tissues which are richest in phos-

phorus, the dominant element in lecithin, are always the most active functionally. This includes the nuclei and nucleoli of animal and plant cells, egg yolk, sperm, roe, nerves; the heart, where it is termed "cuorin," the brain, where it is known as "kephalin," owing to slight variations in chemical structure, etc. As stated by MacLean (39), it occurs in association with the cell protein, permeating it, as stated by Mulon (40), much as a drop of oil permeates paper. Its tenacity therein is so great, according to Mayer and Schaeffer (41) that it is preserved even during extreme emaciation.

The participation of lecithin in thermogenesis is also indicated by many facts. Thus, both Danilewsky (42) and Serono (43) found that small doses of lecithin sufficed to enhance respiratory efficiency. That this is due to oxidation in the tissues is explained by the fact, emphasized by biochemists, that all phospholipoids of the lecithin class are extremely sensitive to the action of oxygen. "Unlike ordinary fats," as stated by Bloor (44), "they are among the most reactive substances found in living beings." MacLean (45), referring to the observations of Thunberg (46) and Warburg (47), states that "this liability of lecithin to oxidation" . . . . "is much increased by the presence of chemical reagents such as iron salts." We are reminded here of the increased catalytic activity that the iron in hemoglobin confers on adrenoxidase—another link for the participation of lecithin in the respiratory process. Such a connection is also shown by the fact that in plants, as observed by Palladin and Stanewitsch (48), the respiratory quotient was materially lowered after they had been subjected to the action of lipoid solvents, thus destroying their lecithin. Finally, the oxidation of lipoids has been found by Vernon (49) to be due to an oxidizing enzyme known as "tissue oxygenase," a term which in itself betokens its unknown origin and which evidently represents my adrenoxidase.

The phenomenal influence of the adrenal cortex on growth when it is the seat of tumors which cause a great increase of its cellular elements, hypernephroma for instance, a little child becoming, within a few years, transformed physically into an adult, finds its explanation in the role of its lecithin in oxidation. In the embryo, as shown by Siwertzow (50) lecithin is

present in relatively large quantities. The adrenal cortex is enormous both in the fetus and during the first months of life. According to Elliott and Armour (51), it contains only lecithin, no cholesterol being present. Lecithin feeding also promotes growth very actively. Frogs' eggs placed in water containing .07 per cent. of lecithin gained 400 per cent. more than others placed in plain water, while embryos fed with eggs, the yolk of which contains lecithin, grew from 67 to 81 per cent. faster than the controls. These observations first recorded by Danilewsky (52) were confirmed by King (53), Johnson (54), and others, who also found that in pups lecithin promoted growth, increased the brain mass, the animals greatly excelling the controls, physically and psychically.

Gudernatsch's observation that giant growth of tadpoles was obtained by feeding them with thymus becomes clear when we realize that the nucleins this organ contains owe their activity to lecithin. Adler (55) caused enormous growth of tadpoles by feeding them with adenoma of the cortex. The influence of cortical tumors upon phenomenal development of the secondary sex characters is also made clear when we recall that the interstitial cells in the testes and ovaries are composed of lecithin.

Deficiency of the adrenal cortex or of lecithin produces contrary effects, ranging from anencephaly to idiocy and dwarfism, general atrophic disorders with hypothermia, low vascular tension, asthenia, etc. Biedl (56) in 1899 found that in some species of fish in which the median or interrenal body is entirely composed of cortical tissue, removal of this organ causes death within three weeks from progressive asthenia. This same course of events occurs in mammals, even, as observed by Elliott and Armour (57) when the medulla is left intact. The need of both the adrenal cortex and medulla to carry on oxidation in the tissues is shown, however, by the fact that destruction of the medulla, in the absence of accessory adrenals, leads to death with similar lethal phenomena.

On the whole, it is difficult to escape the conclusion, even from the few data it is possible to submit in a twenty-minute paper, that *oxidation of the lecithin-phosphorus by the oxygen of the adrenoxidase sustains tissue respiration.*

What is the rôle of cholesterol in this connection?

As far back as 1866 Hoppe-Seyler (58) held that lecithin and cholesterol occur in every animal and vegetable cell, a fact, we have seen, now thoroughly established. There exists, however, considerable confusion concerning the rôle of cholesterol. Probably the most misleading of the functions attributed to it in recent years has been that of acting as an antiseptic. In his elaborate report on the rôle of the lipoids in infection and immunity, prepared under the auspices of the 19th French Congress of Medicine of 1920, the late Prof. Linossier, of Lyons (59), showed conclusively that, quoting his own words, "the general antitoxic rôle of cholesterol is purely a product of the mind." He recalls, however, that while phospholipoids, which include lecithin, render the red corpuscles vulnerable to the hemolytic effects of venoms, cholesterol protects these corpuscles against this action, as well as against that of certain other hemolytic agents. We clinicians can add evidence to these experimental truths, for in pernicious anemia, cancer and other diseases in which hemolysis is evident, one of our sheet anchors is cholesterol. Briefly, the laboratory and the clinic indicate clearly that cholesterol acts in the body as an antihemolytic.

Inquiry as to how this process is carried out, however, again reveals deep obscurity. But once more do we find the explanation in the thermogenic process I have submitted, i. e., that due to the oxidation of lecithin by adrenoxidase. This necessitates, however, as a preliminary to this explanation, an idea of the purpose of the heat energy liberated during this process.

Besides the lipoids found in all cells, these also contain enzymes. In the words of Mendel (69), "enzymes are no longer thought of exclusively as agents of the digestive apparatus; they enter everywhere into the manifold activities of cells in every feature of metabolism." This applies as well to plant physiology, "all known proteolytic enzymes in plants," as stated by Vines (61), "being tryptic." It is here that the heat energy liberated by the oxidizing action of adrenoxidase on the phosphorus of lecithin fulfills its rôle, for, as is well known, the activity of a given enzyme is proportionate up to a certain limit, to the heat energy to which it is subjected. Trypsin, one of the several enzymes present in the tissue cells, for example, stands

heat in the laboratory up to about 104° F., and in the body a somewhat higher temperature.

Fever is the expression of the increased liberation of heat by the adrenoxidase-lecithin reaction, from my viewpoint, the purpose of which is to augment the digestive or proteolytic activity of the cellular trypsin to enable it to destroy by hydrolysis bacteria and their toxins, toxic wastes, etc. When this defensive process becomes too active, as in the liver for instance, where the temperature may reach 106° F., or where the quantitative or qualitative detritus accumulates, as in cancer, the exogenous or endogenous pathogenic factors are not alone destroyed in the process: the red corpuscles, which also contain both lecithin and cholesterol, as we shall see, likewise yield to it, being *digested by the enzymes as if they were themselves pathogenic.* Briefly, they undergo hemolysis.

The need of an antihemolytic to prevent wholesale destruction of the red corpuscles and, I might add, of the tissues themselves, i. e., autolysis, thus asserts itself. As previously stated, this is the function of cholesterol. It follows also from what has already been said, that cholesterol fulfills this all-important rôle by moderating or *restraining the thermogenic activity of lecithin.* It is an *antihemolytic* and *antiautolytic.*

I said "all-important" because we are dealing here with one of the cardinal auto-defensive functions which, neglected as it is, even though I (62) have repeatedly called attention to it, entails the loss of many lives in cardiac, pulmonary and other diseases, owing to the autolytic activity of proteolytic cellular trypsin when subjected to excessive thermogenesis. The protective influence of cholesterol in this connection may be illustrated by various experimental facts. Thus, hemolysis, readily produced by saponin, is prevented by injections of cholesterol, as shown by Kurt Meyer (63) and Mayer and Schaeffer and Terroine (64). Even when given orally, though most active subcutaneously, it is very beneficial in the secondary anemias as observed by Loeper, Farvy and Debray (65).

Pulmonary cavities, as I have long urged, are due to tissue autolysis. Linossier (66) has observed in this disease acute exacerbations of cholesteremia coinciding with the acute febrile exacerbations—an effort of Nature to prevent autolysis of the

pulmonary tissues. In acute infections, a low cholesterol value is the rule during the febrile period following approximately, according to Chauffard, Laroche and Grigaut (67) the temperature curve. When, however, defervescence occurs, the blood cholesterol and the temperature curves run in inverse directions. The cholesterol value recedes, from my viewpoint, because it is no longer needed to curb any excess of thermogenic activity which the lecithin may evoke and thus endanger the blood elements and the tissues themselves.

I could submit many pages of such evidence, all clearly sustaining my opinion that cholesterol owes its established property as an antihemolytic to its inhibitory action on the thermogenic function of oxidized lecithin. It is as such the *systemic antithermic*.

As indicated by adrenals obtained from accident cases, these organs, according to Laroche and Grigaut (68), are the richest of the body in cholesterol. Their content in this lipoid varies greatly, however, under various influences, exertion, disease, the amount and kind of food ingested, etc. This applies also to its relative proportion to the lecithin content. Thus, in the horse, as observed by Mayer, Mulon and Schaeffer (69), cholesterol was found in excess in the cortex when it was enlarged or hypertrophied, while a thin cortex showed a greater abundance of lecithin. These and many other facts have demonstrated that both lecithin and cholesterol fluctuate in the adrenal cortex, and that it constitutes a temporary storehouse for these lipoids, carried thereto, as personal studies have indicated, by leucocytes. At present, cholesterol is attracting the greatest attention, almost to the exclusion of lecithin, but the histological characteristics of both lipoids, and the doubly refractive index of cholesterol clearly indicate that both the latter and lecithin are present.

As to their identity as secretory products of the adrenals, Manasse (70) found large quantities of lecithin in the blood of the adrenal veins soon after birth; Ciaccio (71) identified the lecithin by its specific stains in the adrenal veins also of older animals. Mulon (72) described the lecithin he found in the same veins as a ''lecithalbumin.'' Cholesterol was likewise found in the adrenal veins by Gottschau (73), Biedl (74) and others, in the form of its typical refractive granules, Mulon and Porak

(75) describing them as glia like cells; while Porak and Quinquaud (76) found the proportion of cholesterol much greater in these veins than in the blood, arterial or venous, of any other vessel examined by them. The presence of the medullary secretion, my adrenoxidase, as represented by its familiar active principle, adrenalin, is too well known to require emphasis.

The three products of the adrenals, lecithin, cholesterol and adrenoxidase, are thus secreted into the adrenal veins. How do they reach the tissue cells in which, we have seen, they are to be found? If it is true, as Gley (77) writes, that adrenalin cannot be found in the blood of the inferior vena cava towards which that of the adrenal vein flows, another course must exist as intermediary between the adrenals and the tissues at large. This function appears to me to be carried out by the red corpuscles.

A cardinal fact in this connection is the enormous volume of blood which constantly passes through the adrenals. Entering by way of the many vessels which pierce their capsule, six times the weight of these organs in blood passes through them each minute. This means that the thirteen pounds (6500 grams) of blood which an average human body contains, course through their cellular columns, cortical and medullary, every two hours. This accounts for the kaleidoscopic changes which the cortex may undergo under various influences, including the amount of food ingested, as we have seen. What is the purpose of this phenomenon?

Every up-to-date text-book of physiology calls attention to the fact that besides hemoglobin, the red corpuscles contain lecithin and cholesterol. Under the ultramicroscope, the cobweblike stroma of the corpuscles may be seen to contain luminous dancing balls, their cholesterol, while the lecithin occurs also as bright, but less luminous, droplets. They are closely merged (probably to protect the lecithin from the oxygen of the oxyhemoglobin) with the cholesterol, their normal condition in the corpuscles being, in the words of Hattery (78), that "of a colloid of cholesterol in swollen lecithin," though easily separated by a strong saline solution.

The rôle of these lipoids in the red corpuscles has not only remained unknown, but their presence therein has elicited sur-

prise. This function suggests itself in the light of the data submitted. As is well known, these corpuscles, after emerging from the bone marrow, are active from two to four weeks, or longer according to some observers. Their thermogenic agents, if secreted, must, therefore, be renewed periodically. This function, from my viewpoint, is carried out by the adrenals. In other words, *the adrenals synthetize the adrenoxin, lecithin and cholesterol; the red corpuscles while passing through them appropriate these thermogenic agents, and after passing through the lungs to have their adrenoxin take up oxygen from the air, proceed to the tissue cells.*

It now becomes a question whether the red corpuscles actually supply their thermogenic pabula to the tissue cells. The limits of this paper do not, unfortunately, permit the presentation of histological and biochemical details, but ample evidence exists to the effect that the three secretory products of the adrenals are secreted by the red corpuscles into the blood as needed in the form of droplets, the familiar blood-platelets.

As the red corpuscles do not penetrate to the tissue cells, while, as we have seen, these cells contain the same thermogenic constituents as the red corpuscles, we can only infer, until direct evidence is available, that the corpuscles secrete the blood platelets containing these three agents into the plasma of the capillaries, and then reach the tissue cells by way of their intercellular spaces. We are thus afforded *a chain of structures in physiological sequence, the adrenals, the red corpuscles, the blood platelets and the tissue cells, which all contain the same thermogenic agents, with the adrenals* (as synthetic organs) *acting as source of supply.*

It might appear from the foregoing data that the thyroid plays no rôle in the thermogenic process. In truth, its function is as important as any described, but lack of space permits only the statement here, also based on a comprehensive study, that *the secretion of the thyroid gland is the antagonist of cholesterol in thermogenesis; it increases the lability or sensitiveness of the lecithin phosphorus to oxidation, and thus enhances thermogenesis correspondingly.*

Finally, it might be held that this interpretation of thermogenesis entails the sacrifice of the vast amount of research,

other than endocrinological, on tissue respiration, oxidation and metabolism of over a century. All this work seems utterly wasted and sterile; but this is only because it lacked the foundation which the interpretation I have submitted supplies. Once this is fully developed by cooperation, and adjusted to the present knowledge of tissue respiration and metabolism, the labors of the past will appear in their true light—one which will give clinicians a far better understanding of the pathogenesis of disease, a *sine qua non* of scientific therapeutics.

BIBLIOGRAPHY

1. Editorial: J. Am. Ass. (Chicago), 1919, **72**, 1697.
2. Howell: Text-book of physiology. W. B. Saunders Co., Phila., 1924, 9 ed., p. 903.
3. Halliburton: Text-book of physiology. P. Blakiston's Son & Co., Phila., 1924, 10 ed., p. 392.
4. Sajous, C. E. de M.: Internal secretions and the principles of medicine. 1903, 1 ed., pp. 120-128 & 801-850. Same in 2 ed., 1907, and 3 ed., 1909. In 4 ed., 1911; 5 ed., 1912; 6 ed., 1914; 7 ed., 1916; 8 ed., 1919; & 9 ed., 1921, pp. 56-70 & 801-850. In 10 ed., 1922, pp. 2-8, 59-71 & 801-850. Also, Gaz. d. hôp. (Par.), 1907, 80, 1407; Practitioner (Lond.), 1915, **94**, 179; This Journal, 1917, **1**, 4; ibid., 1922, 6, 197.
5. Lorrain Smith & Haldane: J. Physiol. (Lond.), 1897, **22**, 231.
6. Bohr: Skandin. Arch. f. Physiol. (Berl. & Leipz.), 1891, **2**, 236.
7. Sajous, C. E. de M.: Internal secretions and the principles of medicine. 1903, 1 ed., pp. 120-128; 801-850.
8. Byelaventz: Rousskii Vratch, 1903, **2**, 247.
   Bernstein & Falta: Verhandl. d. deutsch. Kong. f. innere Med. (Wiesb.), 1912, **39**, 536.
   Menten: Am. J. Physiol. (Balt.), 1917, **44**, 176.
   Tompkins, Sturgis & Wearn: Arch. Int. Med. (Chicago), 1919, **24**, 269.
   Sandiford: Am. J. Physiol. (Balt.), 1920, **51**, 407.
   Januschke & Pollak: Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1911, **66**, 205.
   Nice, Rock & Courtright: Am. J. Physiol. (Balt.), 1914, **34**, 326, 331.
9. Kariya & Tanaka: J. Tokyo Med. Ass., 1913, **26**, No. 20; abst., Sei-I-Kwai Med. J., 1913, **32**, 10.
10. Menten & Crile: Am. J. Physiol. (Balt.), 1915, **38**, 225.
11. Menten: Ibid., 1917, **44**, 176.
12. Jackson, D. E.: J. Pharmacol. & Exper. Therap. (Balt.), 1913, **4**, 291.
13. Dixon, W. E.: Brit. M. J. (Lond.), 1902, **2**, 242.
14. Januschke & Pollak: Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1911, **66**, 205.
15. Sajous, C. E. de M.: Internal secretions and the principles of medicine. 1903-1907, **ii**, 822-955.
16. Hoskins, R. G.: Scient. Month. (N. Y.), 1924, **18**, 257.
17. Halliburton: Brit. M. J. (Lond.), 1904 **2**, 444 (Transactions).
18. Sandiford, I.: Am. J. Physiol. (Balt.), 1920, **51**, 407.
19. Mulon: Personal communication.
20. Battelli: Compt. rend. Soc. de biol. (Par.), 1902, **54**, 1179.
21. Jolles: München. med. Wchnschr., 1904, **51**, 2083.
22. Tompkins, Sturgis & Wearn: Arch. Int. Med. (Chicago), 1919, **24**, 269.
23. Israel, J.: Deutsche med. Wchnschr. (Berl.), 1911, **37**, 57.
24. Courmont: Cong. de Méd. Int. (Montpelier), 1898.
    Bra: Cited by E. W. Adams· Practitioner (Lond.), 1903, **71**, 472.
    Jaboulay: Lyon méd., 1897, **84**, 399.
25. Boothby: J. Am. Ass. (Chicago), 1922, **79**, 98 (Discussion).
26. Addis, Barnett & Shevky: Am. J. Physiol. (Balt.), 1918, **46**, 39.
27. Sajous, C. E. de M.: Internal secretions and the principles of medicine, 1903-1922, all ed., pp. 960-1008; Am. J. M. Sc. (Phila.), 1922, **164**, 625.
28. Cannon & Pereira: Prac. Nat. Acad. Sc. (Balt.), 1924, **10**, 274.
29. Hoskins, R. G. & Durrant, E. P.: Am. J. Physiol. (Balt.), 1923, **66**, 176.
30. Hoskins, R. G. & Hunter, E. S.: Ibid., 1924, **70**, 613.

31. Sajous, C. E. de M.: Internal secretions and the principles of medi-
    cine. 1903, **1**, 773.
32. Caskey, M. W. & Spencer, W. P.: Am. J. Physiol. (Balt.), 1925, **71**,
    507.
33. Aub, Forman & Bright: Ibid., 1921, **55**, 293.
34. Bovier & Shevky: Ibid., 1919, **50**, 191.
35. MacLean, Hugh: Lecithin and allied substances. 1918, p. 179.
36. Linossier: Les lipoides. 1920, p. 104.
37. Sajous, C. E. de M.: Internal secretions and the principles of medi-
    cine. 1903, **1**, 518; **ii**, 915.
38. Howell: Text-book of physiology. W. B. Saunders Co., Phila., 1924,
    9 ed., p. 822.
39. MacLean, Hugh: Lecithin and allied substances. 1918, p. 179.
40. Mulon: Cited by Linossier: Rev. gén. d. sc., 1914.
41. Mayer & Schaeffer: Compt. rend. Acad. d. sc. (Par.), 1913, **157**, 156.
42. Danilewsky: Cited by Byla & Delaunay: Les produits biologiques
    médicaux. Paris, 1912, p. 243.
43. Serono: Ibid.
44. ~~~~~~~~~~~~~~~~~~~~~~ Metabolism. D. Appleton & Co., 1922, **3**, 183.
45. ·   and allied substances. 1918, p. 36.
46.   ·   . f. Path., 1909, **23**, 625; Ztschr. f. phys.
    1913, **87**, 82.
47. Warburg: Ztschr. f. phys. Chemie (Leipz. & Berl.), 1913, **87**, 83.
48. Palladin & Stanewitsch: Biochem. Ztschr. (Berl.), 1910, **26**, 351.
49. Vernon, H. M.: Ibid., 1912, **47**, 374; 1913, **51**, 1; 1914, **60**, 202.
50. Siwertzow, D. I.: Biochem. Centralbl. (Berl.), 1904, **2**, 310; St. Petersb.
    Dissert., Wratschebnaja Gaz., 1904, No. 1.
51. Elliott & Armour: J. Path. & Bacteriol. (Edinb.), 1910-11, **15**, 481.
52. Danilewsky, M. B.: Progrès méd., 1896, **24**, 22.
53. King, H. D.: Biol. Bull. (Woods Hole), 1907, **13**, 40.
54. Johnson, M.: Univ. Calif. Pub. Zool. (Berkeley), 1913, **11**, 53.
55. Adler: München. med. Wchnschr., 1922, **69**, 797.
56. Biedl.: Innere sekretion. 1913, **1**, 376.
57. Elliott & Armour: J. Path. & Bacteriol. (Edinb.), 1910-11, **15**, 481.
58. Hoppe-Seyler: Cited by J. B. Leathes: Lancet (Lond.), 1925, **i**, 208,
    803.
59. Linossier: Les lipoides dans l'infection et l'immunité. Paris, 1920,
    p. 98.
60. Mendel: J. Am. M. Ass. (Chicago), 1906, **44**, 843, 944.
61. Vines: Am. Botany, 1901, **15**, 572.
62. Sajous, C. E. de M.: Am. J. M. Sc. (Phila.), 1922, **164**, 625.
63. Meyer, K.: Beitr. z. chem. Phys. u. Path. (Brnschwg.), 1908, **11**, 357.
64. Mayer, Schaeffer & Terroine: Compt. rend. Acad. d. sc. (Par.), 1908,
    146, 484.
65. Loeper, Faroy & Debray: Progrès méd., 1921, **36**, 244.
66. Linossier: les lipoides dans l'infection et l'immunité. Paris, 1920,
    p. 99.
67. Chauffard, Laroche & Grigaut: Ann. de méd. (Par.), 1920, **8**, 69.
68. Grigaut, A. & Laroche, G.: Compt. rend. Soc. de biol. (Par.), 1912, **73**,
    413.
69. Mayer, Mulon & Schaeffer: Ibid., 313.
70. Manasse: Virchow's Arch. f. path. Anat. (etc.), (Berl.), 1894, **85**, 263.
71. Ciaccio, C.: Anat. Anz. (Jena), 1904, **24**, 244.
72. Mulon: Compt. rend. Soc. de biol. (Par.), 1911, **70**, 652.
73. Gottschau, M.: Arch. f. Anat. u. Physiol., Anat. Abt., 1883, 412.
74. Biedl.: Arch. f. d. ges. Physiol. (Berl.), 1897, **68**, 456.
75. Mulon & Porak: Compt. rend. Soc. de biol. (Par.), 1914, **77**, 406.
76. Porak & Quinquaud: Ibid., **76**, 369.
77. Gley: N. York M. J., 1921, **114**, 9.
78. Hattery: Kolloid-Ztschr. (Dresd. & Leipz.), 1920, **110**, 76.

INFLUENCE OF METABOLIC, ENDOCRINE AND NERVOUS FACTORS ON THE ACTION OF INSULIN

B. A. HOUSSAY
Institute of Physiology, Faculty of Medicine
BUENOS AIRES

Insulin produces the disappearance of blood sugar in a way not yet well known. It brings about hypoglycemia (period of descent). Mechanisms that regulate the blood-sugar content are brought into action by this state, diminishing or stopping the descent; the blood-sugar level remains low with small variations in either direction. At a later stage (period of recovery) these mechanisms predominate and the glycemia rises to a normal level, or a little above, and after a few oscillations the normal state is recovered.

The usual factors regulating carbohydrate metabolism are responsible for these reactions; the intenseness of their manifestations is due to the unusual degree of hypoglycemia.

LIVER

. If rabbits are deprived of their glycogen reserves by previous treatment with adrenalin or phlorhizin or through fasting, insulin produces greater and more prolonged descent of blood sugar than in normal controls (McCormick, Macleod, Noble and O'Brien, 1923). This fact has been repeatedly observed.

Hypoglycemia is produced in dogs whose liver has been removed, but recovery is not observed, and is very slow when only a part of the liver remains (Mann and Magath, 1923). In a dog with an Eck fistula, hypoglycemia was produced as in normal dogs, but recovery was not complete for a longer time than usual (Houssay, Sordelli and Mazzocco, 1923).

A decrease in the glycogen content of the liver has regularly been found after insulin action, and is often followed by an increase during the recovery period. Possibly it is transformed into glucose by nervous and humoral mechanisms that will be studied later.

Insulin increases the glycogen content of diabetic animals. In pigeons fed on diets deprived of *B* factor, a similar increase

in the content of the liver and muscles has been observed (Bickel and Collazo, 1923). It is not yet clear whether in normal animals insulin increases the glycogen formation or not.

The effect of fasting has already been mentioned. Bickel and Collazo (1923) and Bickel (1924) have found that pigeons suffering from lack of vitamin B improve when treated with insulin. They believe there was a functional insufficiency of the islands of Langerhans in their animals.

Houssay, Sordelli and Mazzocco (1923) observed rats from two different stocks. One of these presented a poor aspect, thin hair and frequent atrophy of the eyeball. They were very sensitive to adrenalectomy and resisted high doses of insulin. Rats from the second stock were in apparently good condition, having thick, silky coats and clear eyes. Adrenalectomy produced only a small mortality, yet their sensitiveness to insulin was considerably higher than in the first series. Both received as their staple food bread and milk (the milk coming from different dairies). A number of rats from the first stock were kept with those of the second during forty days and so acquired the same fine aspect and increased their sensitiveness to insulin. By adding butter and cod liver oil to the diet of the first stock, unfavorable symptoms disappeared. It was supposed that they had lacked in vitamin A. (Lewis, 1923).

The alkaline reserve has a certain influence on insulin effects. Rabbits fed with green vegetables (cabbages, alfalfa, hay, turnip), giving alkalies and increasing the alkaline reserve, have lower glycemias and more intense symptoms than those fed with acid producing diets (oats, bread) that lower the alkaline reserve (Page, 1923; Blatherwick, Long, Bell, Maxwell and Hill, 1924; Abderhalden and Wertheimer, 1924-1925). Ergotamine does not abolish this increased sensitiveness (Abderhalden and Wertheimer). Burn and Marks (1925) have noticed that in rabbits there is usually an inverse ratio between sensitiveness to insulin and to adrenalin. Rats on diets with little or no carbohydrate are more resistant to insulin, having fewer convulsive symptoms, less marked hypoglycemia and smaller CO_2 output. They respond more readily to adrenalin than normal controls (Abderhalden and Wertheimer).

THYROIDS

The part played by this gland has been studied by observing insulin effects in thyroidectomized animals or after administration of thyroid tissue.

Bodansky (1923) found that simultaneous or previous intravenous injection of thyroxin does not affect hypoglycemia produced by insulin in sheep, but recovery is retarded. If given towards the end of the hypoglycemic state it brings about a pronounced hyperglycemia. These results could be due to the fact that thyroxin stimulates glycogenolysis. In the first case insulin is given to an animal whose glycogen reserves have been diminished by thyroxin. In the second thyroxin rapidly mobilizes glycogen and so increases the blood sugar.

Burn (1923) saw no modification of insulin effect through simultaneous injection of thyroid extract.

Magenta and Biassotti (1923) observed a slightly less marked hypoglycemia in dogs injected with fresh thyroid extract one hour after insulin had been given.

Rats fed with thyroids are more resistant to insulin than normal controls; thyroidectomized rats give the same results in a lesser degree (Houssay and Busso, 1924). Thyroid feeding in rabbits increases resistance to insulin and lowers resistance to adrenalin, always so that no impairment of glycogen reserves is produced. Prolonged thyroid feeding diminishes the glycogen content of the liver and so increases sensitiveness to insulin and diminishes it to adrenalin (Burn and Marks, 1925).

Thyroid insufficiency has a marked effect on insulin action. Thyroidectomy considerably increases sensitiveness; hypoglycemia is established more rapidly, is often more intense and always lasts longer in controls. These facts were observed at the same time by Ducheneau (1923) and Bodansky and have been studied in the following species: rabbits (Ducheneau, 1923; Burn and Marks, 1924-1925); sheep (Bodansky, 1923-24-25); guinea-pigs (Houssay and Busso, 1924; Houssay and Cisneros, 1925). Symptoms are more intense and death is produced by smaller doses in thyroidectomized animals, though sometimes the glycemic level is no lower than in the controls, as has been seen in rabbits (Ducheneau) and rats (Houssay and Busso, Houssay and Cisneros). After thyroidectomy the sensitiveness

to insulin in a given animal increases, especially if previously it was relatively resistant (Brown and Marks).

Several possibilities can explain the facts observed. As thyroidectomized animals have a high glucose tolerance, it could be supposed that after insulin they fix or transform the blood sugar more readily than normal animals. Retarded recovery would be due to a slower reaction in the inverse direction. Not knowing into what compound glucose is transformed by the action of insulin, it is not easy to verify this hypothesis since no quantitative determinations can be made. Glycogen is the only known substance that can be measured in this respect and it is found almost constantly diminished. Thyroidectomized animals may have a slower glycogenolysis, which would explain both the more marked hypoglycemia and the retarded recovery. Their condition would be similar to that of animals deprived of hepatic glycogen as studied by McCormick, Macleod, Noble and O'Brien. This explanation has been supported by Houssay and Busso.

Bodansky attributes delayed recovery in thyroidectomized sheep to absence of thyroid stimulation of glycogenolysis. A normal sheep after an eighteen-hour fast behaves like a thyroidectomized one and conversely a thyroidectomized animal, if it has not fasted, reacts like a normal one.

Increased resistance to insulin caused by thyroid feeding may be due to increased glycogenolysis and lowered carbohydrate tolerance (Houssay and Busso).

Before these hypotheses can be accepted, they must be submitted to experimental proof with simultaneous attention to the effects of insulin on blood sugar and glycogen in normal and thyroidectomized animals fed with thyroid. As many fundamental facts are still unknown, it is possible that these modifications of the insulin reaction may be due to other causes, e.g., alteration in the intermediate carbohydrate metabolism in thyroidectomized animals.

As yet no complete work has been published on the effect of insulin in man. Already in 1923 we proposed the administration of insulin in cases of Basedow's disease with lowered carbohydrate tolerance. Lépine and Parturier (1924), Goffin (1924), Lawrence (1924) have reported good results on some symptoms (insomnia, loss of weight, etc.). Puchulu (1925) ob-

tained no modification in pulse, pressure, glycemia, basal metabolism or menstruation in five cases of hyperthyroidism (or considered such).

After injecting rabbits with parathyroid extract, convulsions are obtained with a third or a quarter of the usual dose of insulin (Winter and Smith, 1923). Feeding parathyroid tablets before the injection of insulin also causes a more rapid and more marked fall of the blood sugar, though parathyroids alone have no effect on glycemia (Forrest, 1923). Dogs without thyroids or parathyroids present a slightly greater hypoglycemia than normal dogs; both experimental and control animals had been fed with calcium up to twenty-four hours before injecting insulin (Houssay and Busso, 1924).

Pituitary extract suppresses insulin hypoglycemia in rabbits (Burn, 1923; Joachimoglu and Metz, 1924; Moehlig and Ainslee, 1925); dogs (Magenta and Biassotti, 1923), and normal and diabetic men (Lawrence and Hewlett, 1925). It raises the blood-sugar level, abolishes symptoms and prevents death. Inorganic phosphorus of blood diminished by insulin is increased by pituitrin (Bollinger and Hartman, 1925). Insulin suppresses the increase of fatty acids in the liver produced by pituitrin (Coope, 1925). Ergotamine suppresses this antagonism between these drugs (Lawrence and Hewlett).

Olmsted and Logan (1923) working with decerebrate cats failed to lower the already high glycemia by injecting insulin. If, while in this condition, the pituitary was removed, hypoglycemia and convulsions were observed; subsequent injection of the pituitrin increased the blood sugar and checked the convulsions for some time and prevented the appearance of symptoms. Bulatao and Cannon (1925) obtained results that differed somewhat from these; insulin produced hypoglycemia in decerebrate cats even when the pituitary had been left untouched. They consider that Olmsted and Logan had too small a number of experiments to draw conclusions from and that their glycemias were within normal limits.

Houssay and Magenta (1924) used dogs whose pituitary had been completely removed some time previously, that had

recovered from the operation perfectly and showed symptoms of glandular removal. In this condition they are extremely sensitive to the toxic and hypoglycemic action of insulin. The blood-sugar level fell rapidly to a low figure and practically no recovery was observed. In toads (*Bufo marinus*) the complete removal of the pituitary produced the same effects; hypoglycemia was more severe and recovery was retarded; lesions of the infundibulum gave similar but less marked results; controls with simple craniotomy or with removal of the anterior lobe only showed normal behavior. The hepatic glycogen was sometimes diminished, but the glycogen content of the muscles did not vary in any of these series (Houssay, Mazzocco and Rietti, 1925).

Several hypotheses can explain these facts: (1) a greater loss of blood sugar to which the prolonged and intense hypoglycemia would be due; (2) a slow glycogenolysis; (3) a lack of hepatic glycogen, though this is not probable as about 1 per cent was found; (4) alterations in the intermediate metabolism (these animals had adiposity, etc.). Further experiments are necessary to clear up the intimate mechanism of the facts observed and to throw light on the different parts played by the pituitary and by the nervous centers surrounding it.

Clinical studies on the subject have not yet been published; only one case of a diabetic with acromegaly has been reported that responded to insulin in the same manner as ordinary cases of pancreatic diabetes (Blum and Schwab, 1923).

KIDNEY

Insulin is excreted by the kidney according to the ratio of absorption; given by mouth 25 per cent is found in the urine (Fisher and Noble, 1923).

The short duration of hypoglycemia after intravenous injection, as compared with subcutaneous administration, might be due to a more rapid excretion of the hormone in the first case. With this in view we asked Magenta (1924) to study the effect of intravenous and subcutaneous injections in nephrectomized dogs. No difference was observed as compared with normal controls (results unpublished).

SPLEEN

Splenectomy in rats does not affect the reaction to insulin (Molinelli, 1924).

PANCREAS

Pancreatectomized dogs survive almost indefinitely when treated with insulin. Fisher (1923) could only obtain a survival of eight months, but Hédon (1924-1925) has a dog living whose pancreas was removed six months ago and Pénaud and Simonnet (1925) have kept dogs in apparently normal condition for more than thirteen months. In the last two papers mentioned the animals were fed with meat and carbohydrate, since a diet of meat alone brings about a loss of weight and less favorable general condition. Hédon also gave pancreas by mouth. One dog went into acidosis and coma on two occasions when insulin was suppressed, but recovered with renewal of treatment and administration of bicarbonate.

Pancreatectomy apparently sensitizes animals to insulin, doses from one-eighth to one-tenth the usual amount producing marked effects (Képinow and Ledebt, 1925). It has often been supposed that insulin stimulates the internal secretion of the pancreas, though up to now no definite proof has been given. Képinow and Ledebt's work is suggestive in connection with this problem.

Depancreatized dogs injected with increasing doses of insulin do not show an increase of sugar transformation in an arithmetical ration with the dose; a logarithmical curve is observed, such that as the dose becomes larger a smaller quantity of sugar per unit is transformed (Allan, 1925).

ADRENALS

Adrenalin has an antagonistic action to insulin; one lowers and the other raises the blood-sugar level. This fact is universally admitted to be true in rabbits (Banting, Best, Collip, Macleod and Noble, 1922; Eadie and Macleod, 1923; Burn, 1923) and in dogs (Magenta and Biassotti, 1923).

Adrenalectomized rats are' more sensitive to insulin (Lewis. 1923) and are killed with one-tenth of the dose fatal to normal controls. Sundberg (1923) obtained similar results in rabbits with both adrenals removed and after suppression of epinephrin secretion. Stewart and Rogoff (1923) in a few experiments on rabbits did not find this increased sensitiveness. In dogs, adrenalectomy greatly increases sensitiveness to toxic and hypoglycemic effects of insulin and recovery, though possible, is much

retarded. Suppression of adrenal secretion by denervation or extirpation of the medulla produces similar though less marked effects (Lewis and Magenta, 1924). Cannon, McIver and Bliss (1923) found greater sensitiveness in cats without adrenal secretion (extirpation of right adrenal, denervation of left adrenal). Recently, Bulatao and Cannon (1925) working with decerebrate cats observed a greater fall in blood sugar on insulin administration after adrenalectomy.

Boothby and Wilder (1923) comparing the calorigenic action of adrenalin and insulin supposed that insulin produced an adrenal discharge. Stewart and Rogoff (1923) could not find this supposed increase of adrenal secretion in cats injected with insulin, but we believe this was due to not having obtained a sufficiently marked hypoglycemia. Cannon, McIver and Bliss showed that when the blood-sugar level dropped below 0.07 per cent in cats with denervated hearts, an increased heart rate is observed, ascribable to increased adrenal secretion, because it does not appear in animals with one adrenal extirpated and the other denervated or when hypoglycemia is avoided by glucose injections. (Hypoglycemia stimulates the adrenal secreting centers.)

Direct evidence of this assertion has been given by Houssay, Lewis and Molinelli (1924). Dogs anesthetized with chloralose were prepared for adrenal transfusion in accordance with Tournade and Chabrol's method, so that all the venous discharge of one adrenal (the left) of the donor is transfused into the jugular vein of the recipient. Under these conditions the blood-sugar level is not raised more than 0.025 per cent in the recipient (nine experiments), but if insulin is injected in the donor and hypoglycemia ensues the recipient has marked hyperglycemia (seven positive results out of eight experiments: 0.064, 0.046, 0.189, 0.293, 0.028, 0.054, and 0.061 per cent increase over the previous level). Denervation of the left adrenal of the donor suppresses this effect in the recipient, although marked hypoglycemia was present in the donor (seven experiments). Finally, when insulin hypoglycemia in the donor is prevented by the injection of glucose only slight hyperglycemia was observed in the recipient (0.021, 0.046, 0.027, 0.019, 0.025, and 0.034 per cent). It seems to us that it has been definitely proved that hypogly-

cemia stimulates adrenal secretion, this being an important factor in the process of the return to the normal blood-sugar level.

Riddle, Honeywell and Fisher (1924) produced hypertrophy of the adrenals in pigeons by repeated injections of insulin.

NERVOUS FACTORS

Hypoglycemia is produced by insulin even if the brain has been removed (Olmsted and Logan, 1923; Bulatao and Cannon, 1925).

In dogs, the splanchnics and the vagi apparently modify the action of insulin in opposite directions. Section of the splanchnics considerably increases sensitiveness to insulin, more so than when adrenal secretion is suppressed by extirpation of the medulla, according to Houssay and Lewis' method (1921). The absence of adrenal secretion is not the only factor involved in splanchnotomy. Section of the hepatic nerves also slightly increases insulin effects. When both splanchnics are cut, therefore, both the adrenal and the glycogenolytic innervation of the liver are interfered with. The splanchnics oppose insulin action by their function of liberating glucose (glycogenolysis) directly through the liver, and indirectly through the adrenals (Lewis and Magenta, 1924). Burns and Marks (1925) also found a greater insulin effect in cats with splanchnics severed.

The vagi have an antagonistic effect. If both vagi are cut just above the diaphragm insulin produces a less marked hypoglycemia and recovery is more rapid than in normal controls (Lewis and Magenta). These nerves have a retarding effect on glycogenolysis. These observations agree with the facts found by Houssay and Lewis (1923) when studying morphine hyperglycemia.

According to Garrelon and Santenoise (1924) insulin is a powerful stimulant of the vagus as shown by a marked increase in the oculo-cardiac reflex (bradycardia, bradypnea, respiratory arhythmia, lower blood pressure) and a greater sensitiveness to peptone shock. These effects can be observed before the modifications in blood-sugar level, but only when pure insulin, free from proteins, is used.

Magenta and Biassotti (1923-24) studied the effects of different drugs on the blood-sugar curves of dogs injected with insulin. The following have a marked and prolonged opposing

effect on insulin action: pituitary extract, picrotoxin, morphia, strychnin, and adrenalin. Potassium chloride, calcium chloride, atrophin and quinine are less active in the same direction and only slight effects were obtained with caffeine, pilocarpin and acetylcholin. Cocaine and sodium chloride had no effect at all. Ergotoxin and bisodium phosphate, on the contrary, favored insulin effects, and to a less extent nicotin, eserin and thyroid extract gave similar results.

Later Mauriac and Aubertin (1924) confirmed the results obtained with atrophin. Labbé and Theodoresco (1924) also found that insulin and caffeine have antagonistic effects on blood sugar and blood pressure. Burn had already described the effect of ergotamin as favoring insulin hypoglycemia.

It can be said that as a rule drugs stimulating the sympathetic, or organs innervated by the sympathetic, tend to counteract insulin hypoglycemia (e.g., adrenalin), drugs inhibiting the sympathetic increase insulin hypoglycemia (ergotamine). Stimulants of the parasympathetic increase insulin effects (eserin, nicotin). But it must not be forgotten that the action of most drugs is complex and difficult to study owing to amphotropism and other causes.

BIBLIOGRAPHY

Abderhalden: Medic. Germ. Hisp. Americana, 1924, No. 10, 833.
Abderhalden, E. & Wertheimer: Arch. f. d. ges. Physiol. (Berl.), 1924, **205,** 547-558, 559-570; **206,** 451-459, 1925; **207,** 222-227.
Allan, F. N.: Am. J. Physiol. (Balt.), 1925, **71,** 472-477.
Banting, F. G., Best, C H., Collip, J. B., Macleod, J. J. R. & Noble, E. C.: Am. J. Physiol. (Balt.), 1922, **62,** 559.
Biassotti, A. & Magenta, M. A.: Rev. Asoc. méd. argent. (Buenos Aires), 1923, **36,** 600; Compt. rend. Soc. de biol. (Par.), 1923, **89,** 1125.
Bickel & Collazo: Deutsch. med. Wchnschr. (Berl.), 1923, **49,** 1408-1410.
Bickel, A.: Munch. med. Wchnschr., 1924, **46,** 1603.
Blatherwick, N. R., Long, L., Bell, M., Maxwell, L. C. & Hill. E.: Am. J. Physiol. (Balt.), 1924, **69,** 155.
Blum, L. & Schwab: Compt. rend. Soc. de biol. (Par.), 1923, **90,** 195.
Bodansky, A.: XI International Physiological Congress, Edinburgh, 21-27, July, 1923.
Bodansky, A.: Proc. Soc. Exper. Biol. & Med. (N. Y.), 1923, **21,** 46; 1924, **21,** 416-417; J. Biol. Chem. (Balt.), 1925, **64,** 56.
Bollinger, A. & Hartman, F. W.: J. Biol. Chem. (Balt.), 1925, **64,** 91.
Boothby, W. M. & Wilder, R. M.: Med. Clin. of N. Am., 1923, **7,** 55.
Bulatao, E. & Cannon, W. B.: Am. J. Physiol. (Balt.), 1925, **72,** 295-313.
Burn, J. H.: J. Physiol. (Lond.), 1923, **57,** 318.
Burn, J. H. & Marks, H. P.: J. Physiol. (Lond.), 1924, **59,** 8; 1925, **60,** 131.
Cannon, W. B., McIver, M. A. & Bliss, S. W.: Am. J. Physiol. (Balt.), 1924, **60,** 46; Boston M. & S. J., 1923, **189,** 14.
Coope, R.: J. Physiol. (Lond.), 1925, **60,** 92.
Ducheneau, L.: Rev. Asoc. méd. argent. (Buenos Aires), 1923, **36** (Soc. Biol., I, 1923, IV, 252); Compt. rend. Soc. de biol. (Par.), 1924, **90,** 248.
Eadie, G. S. & Macleod, J. J. R.: Am. J. Physiol. (Balt.), 1923, **64,** 285.
Fisher, N. F. & Noble, B. E.: Am. J. Physiol. (Balt.), 1923, **67,** 72
Fisher, N. F.: Am. J. Physiol. (Balt.), 1924, **67,** 634-643.
Forrest, D.: Brit. M. J. (Lond.), 1923, **2,** 916.
Garrelon, L. & Santenoise, D.: Compt. rend. Soc. de biol. (Par.), 1924,

90, 470.
Goffin: Le Scalpel, 1924, cit. by Puchulu.
Hedon: Compt. rend. Soc. de biol. (Par.), 1924, 90, 920; 1925, 93, 89.
Houssay, B. A. & Busso, R.: Rev. Asoc. méd. argent. (Buenos Aires), 1924, 30; 7 (Soc. Argent. Biol., 1924, 5, 212); Compt. rend. Soc. de biol. (Buenos Aires), 1924, 91, 1037.
Houssay, B. A. & Cisneros, A. D.: Rev. Soc. Argent. Biol., 1925, 5, 89.
Houssay, B. A., & Magenta, M. A.: Rev. Asoc. méd. argent. (Buenos Aires), 1924, 37 (Soc. Argent. Biol., 5, 389); Compt. rend. Soc. de biol. (Par.), 1925, 92, 822.
Houssay, B. A., Mazzocco, P. & Rietti, C. T.: Soc. Argent. Biol., June 4, 1925.
Houssay, B. A. & Lewis, J. T.: Compt. rend. Soc. de biol., 1921, 85, 1209.
Houssay, B. A. & Lewis, J. T.: Rev. Asoc. méd. argent. (Buenos Aires), 1923, 36 (Soc. Biol., 4, 208); Compt. rend. Soc. de biol. (Par.), 1923, 89, 1120.
Houssay, B. A., Lewis, J. T. & Molinelli, E. A.: Rev. Asoc. méd. argent. (Buenos Aires), 1924, 37 (Soc. Argent. Biol., V, 486); Compt. rend. Soc. de biol. (Buenos Aires), 1924, 91, 1011.
Houssay, B. A., Sordelli, A. & Mazzocco, P.: Rev. Asoc. méd. argent. (Buenos Aires), 1923, 36, 427 (Soc. Biol., 4, 92); Compt. rend. Soc. de biol. (Buenos Aires), 1923, 89, 744.
Joachimoglu, G. & Metz, A.: Deutsch med. Wchnschr. (Berl.), 1924, 50, 1787.
Képinow, L., Ledebt, S.: Compt. rend. Soc. de biol. (Par.), 1925, 93, 16.
Labbé & Theodoresco: Ann. Med., 1924, 16, 211.
Lawrence: Brit. M. J. (Lond.), 1924, No. 3330, cit. by Puchulu.
Lawrence, R. D. & Hewlett, R. F. L.: Brit. M. J. (Lond.), 1925, No. 3361.
Lépine & Parturier: Compt. rend. Soc. de biol. (Par.), 1924, 90, 269.
Lewis, J. T.: Rev. Asoc. méd. argent. (Buenos Aires), 1923, 36 (Soc. Biol., 4, 203); Compt. rend. Soc. de biol (Par.), 1923, 89, 1118.
Lewis, J. T. & Magenta, M. A.: Rev. Asoc. méd. argent. (Buenos Aires), 1924, 37 (Soc. Argent. Biol., 5, 370); Compt. rend. Soc. de biol. (Par.), 1925, 92, 821.
McCormick, Macleod, Noble & O'Brien: J. Physiol. (Lond.), 1922, 57, 234-252; Am. J. Physiol. (Balt.), 1923, 63, 189.
Magenta, M. A. & Biassotti, A.: Rev. Asoc. méd. argent., 1923, 36, 600 (Soc. Biol., 4, 192, 262); Compt. rend. Soc. de biol. (Par.), 1923, 89, 1125; 1924, 90, 249.
Mann & Magath: Am. J. Physiol. (Balt.), 1923, 65, 403.
Mauriac, P. & Aubertin, E.: Compt. rend. Soc. de biol. (Par.), 1924, 89, 38.
Moehlig, R. C. & Ainslee, H.: J. Am. M. Ass. (Chicago), 1925, 84, 1398.
Olmsted, J. M. D. & Logan, H. D.: Am. J. Physiol. (Balt.), 1923, 66, 437-444.
Page: Am. J. Physiol. (Balt.), 1923, 66, 1-4.
Pénaud, H. & Simonnet, H.: C. R. Acad. Sciences, 1925, 180, 702-704.
Puchulu, F.: Rev. Asoc. Med. Interna (Bs. As.), 1925, 6, 140.
Riddle, O., Honeywell, H. E. & Fisher, W. S.: Am. J. Physiol. (Balt.), 1924, 68, 461.
Stewart, G. N. & Rogoff, J. M.: Am. J. Physiol. (Balt.), 1923, 65, 331.
Stewart, G. N., & Rogoff, J. M.: Am. J. Physiol. (Balt.), 1923, 65, 342.
Sundberg, C. G.: Compt. rend. Soc. de biol. (Par.), 1923, 89, 807.
Winter & Smith: J. Physiol., 1923, 58, 108-110.

A CASE OF PRECOCIOUS AND HEREDITARY DIABETES INSIPIDUS

G. MARANON and E. BONILLA

Department of Medical Pathology of the General Hospital of Madrid

Diabetes insipidus occurs chiefly in the early stages of life. In a book published by one of the authors of the present paper (Marañon, 1920) we reported statistics of 35 cases observed personally, of which 75 per cent showed commencement of the process before the patients were 10 years old. Since then we have seen 15 more cases which maintain the same proportion.

Within this period the most favorable age for commencement of polyuria is that of the years immediately preceding the coming of puberty. It is very uncommon that this process begins in the first two years of a child's life and it is this circumstance which induces us to publish the case referred to in this paper.

Deluca (1915) has recently reported a case of diabetes insipidus which started at three months; we understand that this is the earliest mentioned in the literature. Delafield and Rachel (quoted by Rathery, 1912) mention a case in a child of six months; Variot speaks of one of seventeen months (quoted by Rathery) and Pincherle and Magni (1924) in a paper on juvenile diabetes insipidus published a few months ago and which constitutes one of the most important documents related to this disease, refer to a case in which polyuria began toward the end of the first year and another case at seven months. In our patient the polyuria started at twelve months.

The clinical history is as follows:

M. V., 20 months old. Both parents are healthy but, according to the father of the child, *its mother had experienced on several occasions before and after marriage periods of insistent thirst and considerable polyuria; but nothing abnormal was found on analysing the urine.* We were unable to see her, but the data given, appears to correspond perfectly to attacks of diabetes insipidus. They have another child, six months old, who is normal. The mother has had no abortions or other symptoms indicative of syphilis and the pregnancy and parturition of the patient were normal. The child was

born at term, of normal weight and appearance but with two teeth erupted in the lower jaw. The mother nursed the child for the first month, afterwards giving it condensed milk and later ordinary milk, which is the only food which it takes at present. It began to walk at fourteen months and has not had any other illness.

Eight months ago, that is when it was one year old, the parents began to observe that it passed very much urine and frequently cried for water. Since then both symptoms have increased.

At the present time the child weighs eight kilograms, is seventy-five centimeters tall and presents a normal aspect, as can be seen

from the photograph. The upper jaw has a complete set of teeth, but the lower jaw has only the two teeth which it had at birth. The child walks well, can speak a few words and its intelligence is normal for its age.

The urine output reaches eight liters in twenty-four hours, the child drinking about the same amount of water. The analysis of the urine gives the following data: Specific gravity, 1.004; chlorides 1.1; urea, 1.95; absence of abnormal substances.

An injection of half a cubic centimeter of pituitrine brought the polyuria down to four and one-half liters on the following day, when only four liters of water was drunk, and the child slept several hours on end without being awakened by thirst. Forty-eight hours later the polyuria and thirst again reached their former level. Another injection of one cubic centimeter of pituitrine brought the polyuria down to three and one-half liters and the water drunk to three liters. The injections were repeated on several other occasions, but only transitory improvements were obtained.

Each micturition consisted of about five hundred cubic centimeters which, considering the size of the child, signifies an enormous dilatation of the bladder.

It presented no nervous symptoms nor the slightest sign of hypophyseal or para-hypophyseal lesion. The radiographic examination of the sella turcica, which had to be repeated several times on account of the child's moving, presented a completely normal outline.

As an interesting comment on this case, we draw attention to the polyuria of the mother. All writers on this subject have laid emphasis on the importance of the hereditary factor in diabetes insipidus. Weil (1884, 1908) describes a family of 78 members, of whom 23 suffered from polyuria, and quotes several other cases of transmission of the process from one generation to another and sometimes to the third generation. Lancereaux (1869) found eleven cases of positive inheritance in a group studied and Van der Heijden (1875) mentions ten observations of hereditary diabetes insipidus in a similar collection of data.

In our above-mentioned book (1920) we drew attention to the fact that this preference of hereditary ethiology is an argument in favor of the endocrine nature or, more correctly speaking, of the hypophyseal nature of diabetes insipidus, since the hereditary transmission of a determined endocrine predisposition is a common and established fact whilst, on the contrary, a lesion of the nervous system localized in such an exceptioned position as the *infundibulum* is always a casual occurrence.

With respect to the pathogeny, as we have indicated, the child *showed no symptom imputable to a lesion of the hypophysis*. It was of average height, had no inclination to adiposity and there were no clinical or radiological symptoms which would induce one to suggest a lesion of the hypophysis or the contiguous parts of the nervous system. However, we are still more convinced every day, that only a very careful anatomical, macroscopical and histological examination would enable one to speak of the existence or non-existence of lesion of the hypophysis and of the para-hypophyseal centers.

As it is our aim to present a case of juvenile hereditary diabetes insipidus, we are not taking part in the agitated discussion of the mechanism of this disease. The publication of our book to which we have referred above and a later monograph (1921) has placed us in the position of definite proponents of the hypophyseal theory, and in consequence we have been the object of criticisms in late years, some friendly and others not so, by almost all authors who have devoted themselves to this illness, as nearly all are today inclined towards the exclusively nervous theory.

We shall shortly discuss this question again, giving our experience of the last few years. For the moment we will simply state that we have never denied the intervention—undeniable with our present knowledge of science—of the polyuric centers in the genesis of this disease. *From the very first we were in favor of the eclectic theory,* which was at the same time supported by Pende (1915) and other authors at a later date and which laterly tends to be confirmed by the research of histologists, who offer objective evidence of the passage of the hypophyseal colloid through the pituitary stem as far as the region of the middle ventricle. But within this eclectic theory, we insist on the important of the internal secretion of the hypophysis, the intervention of which is based on facts which have not yet been refuted. We therefore endorse the conclusion in which Pincherle and Magni sum up their work as follows: "In this way from Pende to Marañon, from Falta to Loewy, the neuroglandular conception of diabetes insipidus is gaining ground and taking on a definite signification which appears to us should serve as a basis for the interpretation of the pathogenic mech-

anism of this disease, admitting that the mesencephalic centers and the hypophysis, disturbed separately or together, may have a reciprocal influence on each other, contributing to the complex disturbance of the water and salt, renal and extra-renal metabolism, which is the basis of the so-called polyuria insipidus."

BIBLIOGRAPHY

Deluca: 1915. Semana méd. (Buenos Aires), 325.

Lancereaux: 1869. Thése d'agregation, Paris.

Marañon: 1920. Neuvas orientaciones sobre la patogenia y el tratamiento de la diabetes insipida. Madrid.
    1921. This Journal, 5, 159.

Pende: 1915. Endocrinologia (Milano).

Pincherle & Magni: 1924. Arch. di patol. e clin. med., 3.

Rathery: 1912. Diabetes insipides. Manuel d. Mal. de la Nutrition. Devobe, Archard & Cartaigue, Paris.

Van der Heijden: 1875. Inaug. Dissert., Berlin.

Well, J.: 1908. Arch. f. klin. Med. (Berl.), 93.

Weil, S.: 1884. Arch. f. path. Anat. (etc.), (Berl.), 95.

THE INFLUENCE OF DESICCATED SPLEEN AND BONE MARROW FEEDINGS UPON THE ERYTHROCYTE AND HEMOGLOBIN CONTENTS OF THE BLOOD

SHEPARD SHAPIRO, M. D., and FLORENCE HULTON
FRANKEL, Ph. D., M. D.
From the Division of Laboratories and Department of Medicine,
Montefiore Hospital,

NEW YORK CITY

According to Jordan (1) the spleen is phylogenetically both a myeloid and a lymphoid organ. Beginning with the reptiles it loses both these functions to the bone marrow and lymph glands, respectively. Embryologically it is essentially erythro-·cytopoietic. In man it possesses this function until about the fifth month of embryonic life, when the bone marrow becomes the chief seat of red blood cell formation. The spleen, however, persists throughout life, and the question therefore arises, what function does it then perform, if any?

Jordan (1) further suggests that in spite of its large size, the spleen persists in mammals as a phylogenetic remnant without essential function. It is believed, however, that in the adult mammal the spleen plays a part in blood cell formation. Lymphocytes are abundant in the Malpighian corpuscles and may be present in the splenic vein in relatively large numbers (as much as one to every 4 red cells), so that it is believed that the spleen is a seat of lymphocyte formation. In the frog the greater portion of the spleen is made up of lymphocytes. Jordan and Speidel (2) have demonstrated that it is in these animals the chief source of erythropoiesis (with the exception of a short post-hibernation period when the bone marrow functions), and that it functions by producing lymphocytes which, in turn, differentiate into erythrocytes. On evolutionary and embryonic grounds, therefore, it would be logical to seek in higher animals for evidences of influence of splenic function upon erythrocytopoiesis.

In 1895 Danilewsky and his pupil Salensky (3), on the basis of previous work of others who claimed to have observed

anemia following splenectomy, expressed the belief that the spleen may stimulate the production of erythrocytes by the bone marrow. Studies were, therefore, made of the effects of extracts of spleen tissue upon the red cell content of the blood. Krumbhaar and Musser (4) in 1914 were able to confirm previous workers (3) (5), that following the intraperitoneal injection of fresh saline extracts into dogs there occurred an increase both in the erythrocytes and hemoglobin in the blood which lasted 1 to 2 days. They reported also that the feeding of raw beef spleen to dogs did not prevent the secondary anemia which they found to occur after splenectomy in these animals. The results with saline solution of spleen were confirmed by Downs and Eddy (6) in rabbits. These workers emphasized the appearance of reticulated and nucleated corpuscles in the blood stream. The assumption has been, therefore, that the spleen liberates a hormone which influences the activity of the erythrocytopoietic tissues.

Downs and Eddy (6) found evidence that the spleen exerted a haemolytic effect, especially upon the older and the less resistant red cells, and that the spleen at the same time stimulated the bone marrow to produce fresh erythrocytes to compensate for those destroyed. Using virtually this same working hypothesis, Leake (7) (8) and his associates have studied the effects of the administration of extracts of bone marrow and spleen upon the cell content of the circulating blood. Confirming those already mentioned, they found that spleen extracts caused, following a transient fall, an increase in the number of circulating red blood cells and that saline extracts of bone marrow also caused a rise in the number of erythrocytes. They observed, further, moreover, that a combined extract of both spleen and bone marrow caused a more pronounced increase in the number of circulating red blood cells than did either extract given alone. The combined extract also caused a rise in the hemoglobin percentage of the blood.

These findings were then applied clinically by Leake and Evans (9). Kay (10), Thalheimer (11), Dunham (12), Fisher and Snell (13) and others. Each of these authors reports practically the same results: a gradual increase in the erythrocyte count and rise in the hemoglobin content of the blood during

the period of feedings. The preparation used by these authors was desiccated spleen and bone marrow, equal parts, in doses of about 15 grains (1 gram) daily.

We have been studying the effects of spleen and bone marrow feedings in a series of cases observed over long periods of time (6 months) in an effort to observe the comparative responses of alternate feeding and withholding of the preparation. Our series consisted of 8 cases. Owing to the appearance of complications, four of the individuals were dropped. The patients were all male inmates of Montefiore Hospital who had been in the institution for a number of months. Patient 1 was 63 years old. He had chronic cardiac disease. Number 2 was a patient 27 years old, who had chronic hip disease. He was afebrile during the experimental period. Number 3 was 48

CASE 1

years old. He suffered from chronic hypertension and hemiplegia. Number 4, 18 years of age, was incapacitated by reason of chronic osteomyelitis of the femur. It should be emphasized that these cases were particularly well suited for the experiment by reason of the fact that their diets and muscular activity were fairly constant over a period of months, both before and during the experiment. The preparation used was, as described above, desiccated spleen and bone marrow* in doses of 1 gram (5 grains, t.i.d.) daily. The blood counts were made three times in a week. The blood was taken at the same time of the day

(11 A. M.) to eliminate the effects of factors which may influence the cell content of the blood, such as digestion. The counts were made in duplicate by the same person (F. H. F.). The hemoglobin determinations were made with a Tallquist hemoglobin scale.

The following plan was used. A series of control counts was made before the medication was started. The feedings were continued for several weeks, withheld for a few weeks, then resumed again for about one month and then again stopped. In three of the cases desiccated thyroid (2 grains daily) was administered at the end of the experiment for purposes of comparison with the spleen-bone marrow effects. In 3 of the 4 cases in response to the first feedings there occurred, commenc-

CASE 2

ing within 3 days, a gradual increase in the erythrocyte count of the blood of about 600,000 to 800,000 cells per cubic millimeter of blood, which level was more or less sustained during the time the feedings were continued. In the one case (Number 3) there was an increase of about 200,000 cells per cmm. of blood during the first period of spleen-bone marrow feedings. As soon as the preparation was withheld the red cell counts fell in each case to approximately the fore period levels with the exception of case Number 3, in which instance it fell to below this level. The hemoblogin response was parallel to that of the red cells but usually more marked. After the feedings were resumed a second time the reactions were practically the same in c.

case as during the first feeding period, with a tendency toward
a slightly more pronounced response. The hemoglobin increase
was parallel with that of the red cells, slightly more striking in
three of the cases and less in one (Number 2) during the sec-
ond feeding period. Thyroid administration caused no change
in 2 cases and a rise in one case, which was not sustained in
spite of continuation of the feedings.

It was suggested that during the feeding periods there
might be a rise in heat production accompanying the increase in
erythrocytes. In no case, however, did we find the basal metabo-
lism to be increased. The preparation was administered also in
3 cases of pernicious anemia. In none of these did any note-
worthy change occur in the red cell or hemoglobin content of
the blood.[*]

DISCUSSION

If it can be definitely established that extracts of spleen
and of bone marrow possess an active substance which may in-
crease the production of erythrocytes it would be of great value
both to the physiologist and to the clinician. It would be evi-
dence of an additional splenic function in the adult mammal,
and it would also offer a conception of how the production of
erythrocytes may be controlled. To the clinician it would pre-
sent a ready means for increasing the erythrocyte and hemo-
globin content of the blood.

_____

[*]This work was done in conjunction with Dr. E. A. Leadbeater of
the medical service of Montefiore Hospital.

The experimental evidence published from various sources is in general agreement that saline solutions of spleen extracts cause a temporary fall followed by a more prolonged rise in the erythrocyte content of the circulating blood. The evanescent decrease is probably evidence of the hemolytic action which is known to be possessed by the spleen. The stimulating effect upon erythrocytopoiesis is apparently more constant and more powerful.

The further development of this by Leake and his associates which has led to the clinical work with spleen and bone marrow extracts, while still a hypothetical consideration, seems very much in the realm of possibility, as shown by their own experi-

mental observations as well as the clinical reports mentioned above. Our findings confirm the claim that spleen-marrow extract is a stimulant to erythrocytopoiesis. We find that the increase in red cells lasts only as long as the feedings are continued and that at the same time there is a concomitant and usually more marked rise in the hemoglobin content of the blood. There is no change in heat production caused by this extract. The preparation is without effect when administered in cases of pernicious anemia.

CONCLUSION

An extract of desiccated spleen and bone marrow was alternately fed and withheld in a series of 4 cases over a period of 6

months. During the periods of feeding there occurred increases in the erythrocyte and hemoglobin contents of the blood which returned to about the pre-feeding level when the preparation was withheld.

BIBLIOGRAPHY

1. Jordan, H. E.: The significance of the spleen, in the light of embryological, evolutionary and experimental data. Virginia M. Month. (Richmond), 1924, **51**, 537.
2. Jordan, H. E., & Speidel, C. C.: Studies on lymphocytes. IV. Further observations upon the effects of splenectomy in frogs. J. Morphol. & Physiol. (Phila.), 1925, **40**, 461.
3. Danilewsky, B., & Selensky, M.: Ueber die blutbildende Eigenschaft der Milz und des Knochenmarks. Arch. f. d. ges. Physiol. (Berl.), 1895, **61**, 264.
4. Krumbhaar, E. B., & Musser, J. H., Jr.: The relation of the spleen to blood destruction and regeneration and to hemolytic jaundice. X. Concerning the supposed regulatory influence of the spleen in the formation and destruction of erythrocytes. J. Exper. M. (Balt.), 1914, **20**, 108.
5. Simon, J., & Spillman, L.: Recherches expérimentales sur l'action des injections d'extrait de rate. Réaction du sang. Compt. rend. Soc. biol. (Par.), 1906, **60**, 833.
6. Downs, A. W., & Eddy, N. B.: The influence of splenic extract on the number of corpuscles in circulating blood. Am. J. Physiol. (Balt.), 1920, **51**, 279.
   Further observations on the effects of the subcutaneous injection of splenic extract. Am. J. Physiol. (Balt.), 1922, **62**, 242.
7. Leake, C. D., & Leake, E. W.: The erythrocyte action of red bone marrow and splenic extracts. J. Pharmacol. & Exper. Therap. (Balt.), 1923, **22**, 75.
8. Leake, C. D.: The hematopoietic effects of desiccated red bone marrow and spleen in normal humans. J. Pharamacol. & Exper. Therap. (Balt.), 1923, **22**, 401.
9. Leake, C. D., & Evans, J. S.: A preliminary note on the use of red bone marrow and spleen in the treatment of anemia. Wisconsin M. J. (Milwaukee), **22**, 294.
10. Kay, H. M.: Clinical experiences with desiccated spleen and red bone marrow in the treatment of anemia. Medical Journal and Record (N. Y.), 1924, **120**, 281.
11. Thalheimer, W.: Use of desiccated red bone marrow and spleen in treatment of anemia. J. Lab. & Clin. M. (St. Louis), 1924, **10**, 129.
12. Dunham, R. W.: Spleen extract and bone marrow in the treatment of tuberculosis. Wisconsin M. J., (Milwaukee), 1924, **33**, 292.
    Effect of spleen extract and bone marrow on the blood picture in pulmonary tuberculosis. Am. J. M. Sc., 1925, **170**, 394.
13. Fisher, D., & Snell, M. W.: Spleen extract and bone marrow in the treatment of secondary anemia. Wisconsin M. J. (Milwaukee) 1924, **23**, 286.

NEW THEORY OF THE FUNCTION OF THE PROSTATE DEDUCED FROM GLAND TRANSPLANTATION IN PHYSICIANS.*

H. LYONS HUNT, M. D., L. R. C. S., EDINBURGH

Associate Surgeon, New York Polyclinic Hospital, Consultant on Plastic Surgery, Midtown Hospital.

NEW YORK

The first report which I made on this subject was published in *Endocrinology* in 1922 (1). This was a report of three cases of gland transplantation, the first being that of E. W. K., who following a sudden mental shock became completely impotent. Glandular extracts and aphrodisiacs produced no beneficial results. The impotence was associated with considerable debility, weakness in the lower extremities and insomnia. It was determined to try gland transplantation, and through the courtesy of the laboratories of Armour and Company, a fresh testicle of a ram was secured. This was received in a refrigerated state and was refrigerated further in boric acid for thirty hours more before the transplantation. A longitudinal section 1 cm. in thickness was made and embedded in the patient's abdominal wall. Although this gland became necrotic and began to slough away the patient began to have erections nine days after the operation. Normal sexual life, and increased appetite and a general feeling of well-being ensued, all of which the patient attributed to the operation. The results in this case encouraged me to make a further trial of gland transplantations and the next two cases were reported with the one above outlined.

A second article consisted of a general review of the subject with conclusions from the results of 127 gland transplantations. Since making that report I have continued to perform the operation and my series now totals over 300 cases.

In the earlier cases the transplants were, in the male, sliced grafts of the testicle of various animals, chiefly the young bull and the ram. In women the operation consisted in placing in a

phy such as takes place in the ovary consists of diminution of the size of an organ or of its tissues, without marked alteration in structure, and it may finally disappear altogether. Other degenerative changes may be associated. The ·cytoplasm of atrophic cells is often more transparent than normal, and may contain an undue amount of pigment. The parenchyma cells in the generative gland become smaller and may be more or less pigmented. Thus we see in the female at the menopause we have a marked fibrosis of the ovary, and also of the uterus, at the time these organs lose their function. In the male the testicle usually undergoes a certain amount of diminution, and there is an onset of either partial or complete impotence, but always do we note in the male a certain amount of hypertrophy of the prostate. *This hypertrophy is not a true hypertrophy but a hypertrophic atrophy.*

In discussing the mechanism of prostatic hypertrophy Tanenbaum says it is usually conceded that the term prostatic hypertrophy does not cover the pathological process intended to be conveyed by this term. Recent writers, as for example, Fischer, have furnished convincing evidence that it is not the prostate which undergoes hypertrophy. Tanenbaum calls attention to a group of glands described by Littré and Leydig and Aschoff as peri-urethral or submucous glands, which apparently undergo proliferation in later life. The prostate, in contradistinction to the submucous glands,·undergoes presenile changes similar in character to those observed in other organs in advanced life, while the submucous glands undergo hypertrophy. Simmonds is of the opinion that these changes are brought about by the internal secretion of the preserved testicular substance, which in association with the primary atrophy of the prostate, stimulates the peri-urethral glands to proliferate. In proliferating these peri-urethral glands spread in various directions and thereby protrude upon the prostate gland, which in consequence of compression undergoes further atrophy. Another reason, Tanenbaum continues, why the term hypertrophy is a misnomer is that it denotes a simultaneous enlargement of the various structures of an organ. Such a process is generally not observed in pure prostatic hypertrophy, which exhibits hyperplasia of the glands with no deviation from the normal structures.

These considerations justify the definition of prostatic hypertrophy as a nodular hyperplasia of the peri-urethral glands which are located between the veramontanum and the internal sphincter. It is only with the secondary changes elicited by the growth in the neighboring organs and with the appearance of obstruction that the true pathological condition begins. Delafield and Prudden state that microscopical examination of the hypertrophied prostate shows a considerable variety of pictures. The gland may be converted into what is practically a multilocular cyst, or the fibrous tissue may undergo a great hyperplasia without marked increase in the glands. The hyperplasia may be diffuse or nodular. The interstitial tissue, especially about the gland, is usually infiltrated with lymphocytes and occasionally this infiltration is quite diffuse. When the hypertrophy of the gland is circumscribed nodules of muscle and fibrous gland tissue which are formed near the periphery of the organ may project into the bladder, and even become detached and be found as small movable tumors beneath the mucous membrane.

This hypertrophy of the prostate occurs too often with the onset of impotence or diminished function to be attributed to mere coincidence. It occurs so often that we are compelled to draw the conclusion that the prostate is definitely responsible, *with the testicle,* for, both sex function and sex desire. The following case offers evidence in support of this idea.

Mr. C. L. G., a bank president, aged 57, an American, was normal in every way except that for thirteen years, or from the age of 44, he was compelled to use a catheter because of an enlarged prostate. Sex function and sex desire during this thirteen years was diminished. On Feb. 5, 1923, prostatectomy was performed. Following this operation sex desire and sex function were completely lost. On June 14, 1923, a slice of ram's testicle was transplanted according to the old technic. The gland sloughed out and the results were negative. On July 13, 1923 a second gland transplantation was performed, which was a take; i. e., it did not slough out. But no result on sex function accrued. On Nov. 20, 1923, another attempt at gland transplantation was made. This time a section of bull's prostate was employed. This gland sloughed away, but during the period of necrosis the patient experienced sex desire and erection. Owing to the fact that this gland sloughed away another attempt was made on April 30, 1924, the effects of which were negative. Finally, on June 3, 1925, a fifth gland transplantation was undertaken. This attempt, like the former ones, was unsuccessful. Going more into detail in this case, the patient came for one definite purpose, namely to recover his sex life. He was a man about 6 feet 1 inch in height, weighing approximately 240 pounds, obese. anemic, his mind functioning sluggishly. It will be seen from the above operations that

the transplantation of testicular tissue was a "take" in one instance; that is, it did not slough away. Its effect on the sex organs, however, was nil. But, on the other hand, its effect on the man's general vigor, metabolism and mental activity was remarkable. He lost approximately 60 pounds in weight, his anemic appearance vanished, and from being sluggish he became active in every way except in the way he desired. He improved to such an extent that his physician insisted on his return for a further gland transplantation, hoping that the impotence, which was his chief complaint would disappear. Only in one instance did the return of potency manifest itself and this was immediately following the transplantation of the prostatic tissue.

I then decided to give to all patients in whom I transplanted testicular tissue prostatic extract in tablet form. No better results were obtained by this measure than before its adoption. A watery solution of prostatic extract was prepared but was found to give a precipitate upon the addition of $1:10,000$ hydrochloric acid, hence giving prostatic extract by mouth seemed to be inadvisable. Several laboratories were asked to prepare prostatic extract in ampoule form to be given hypodermically. The laboratory of Lilly and Company, after many months of work, finally supplied me with several hundred ampoules which I have been using this year in those cases of testicular transplantation which showed no ·definite results within three weeks following the transplantation. The effects have been rather remarkable. I have had not one case which did not show a return of sex function when prostatic extract was given hypodermically in conjunction with testicular transplantation.

As stated in the title, this paper is devoted to observations which I have made in those cases in which testicular or ovarian transplantations have been made in physicians or physicians' wives, since it would seem that the information as to results obtained from this source might be regarded as more definite and reliable than that obtained from lay patients.

The first case is quoted out of order so far as the transplantation is concerned, for the reason that it bears out the hypothesis that prostate hormone is important.

Case 1. This patient, whom we shall call Dr. A., was in his seventieth year, a Harvard graduate, a member of the American College of Surgeons, the New York Academy of Medicine, and a consulting surgeon to four of New York's largest hospitals. He complained of prostatic hypertrophy, impotence, debility and nocturnal urination (four times nightly). On July 23, 1925, gland transplantation was performed. There were no immediate effects. About two weeks after the operation prostatic extract was administered hypodermically. On August 10th the patient reported that following

the hypodermic of prostatic extract he was called upon to urinate but once during the night. On September 15th he reported that all his old lassitude had disappeared, that he had been aroused only once nightly to urinate since August 10th, that he noticed a definite improvement in his sight, that he now awakens daily with an erection, and that he had succeeded in having definite normal sexual intercourse and an orgasm. An experience that had not happened for many years.

Case 2. Dr. B., aged 62, a practitioner of New York, a member of the American College of Surgeons, the New York Academy of Medicine and the American Medical Association, a graduate of Columbia University, complained of complete impotence and general debility. Testicular tissue from the ram was transplanted on Oct. 20, 1924. The patient reported a "tonic" effect but no influence on the sex glands. He has received a second transplant.

Case 3. Dr. C., aged 53, a graduate of Drake University, College of Medicine, came from a western state to consult me because of marked debility, impotence, diabetes, sciatica and intercostal neuritis. This case was one of those that are rather bizarre in their results. This patient gave the history that in 1918 or 1919, during the influenza epidemic, he was practicing in a small western town where, due to overwork, exposure and loss of sleep, he suffered a breakdown, and he also developed influenza. His recovery from this condition was slow and was followed by the onset of diabetes mellitus and an associated neuritis, which compelled him, in 1920, to give up his work entirely. Since that date to the time of his arrival in New York for gland transplantation on Nov. 20, 1924, he had dissipated his entire savings in seeking suitable climatic conditions and sanatorium treatment to improve his condition. Removal of his gall-bladder in Rochester, Minn., was not followed by any improvement, and when he arrived in New York his condition was such that he was able to ambulate only with the assistance of a crutch and cane. Because of his condition I felt hesitant about operating and called in consultation Dr. Otto von Huffman and Dr. A. J. Gelarie before proceeding to transplant testicular tissue. On the advice of these consultants the transplantation was made on Nov. 22, 1924. Within a fortnight the patient made the following report: "I have done away with my crutch and cane entirely. For the first time in four years I am free from pain and for the first time in many months I have been able to concentrate sufficiently to read a newspaper, which I have not been able to do because of the severity of my pain." When the patient came to my office the improvement in his appearance was so marked that it would have to be seen to be appreciated. In spite of the fact that part of the glandular tissue underwent necrosis after operation, the results seemed to be successful. I received a letter from him dated March 9. 1925, in which he stated that he had returned to his practice, and that he wished to have the details of the technic I had used on him as he intended to transplant glandular tissue in a number of cases he was treating.

Case 4. Dr. D., aged 52, a graduate of the Women's Medical College of Baltimore. complained of asthenia, debility, obesity. anemia, hot flashes and the usual symptoms of the menopause. The urine contained albumin, hyaline casts, pus and epithelial cells. The hemoglobin was 75 per cent; red blood cells. 4,000.000; leukocytes, 7.000. The pulse was 65, the temperature 97° F. The stools were negative. A transplantation of ovarian tissue from the sheep was performed on Dec. 6, 1923. The results were negative and the operation was repeated on Oct. 20, 1924. In a letter dated March 22, 1925, this woman physician writes: "I have noticed that this is the first winter

in the past twenty-five years that I have not had subnormal temperature and have consequently not suffered from cold. My pulse rate also has been higher; it was formerly 60 to 65°, while it is now 74. My blood hemoglobin was 65; it is now 87. My heart and kidneys are both better. The asthenia is seldom present, and then only following marked exertion. I am sleeping wonderfully well. There is no change in the sex condition. The hot flashes have disappeared." This patient has referred a number of patients to me from her own practice. One of these who received gland transplantation two years ago has referred her daughter to me this year for the same operation.

Case 5. Dr. E., a man who holds a chair at the New York Post-Graduate Medical School, after submitting to gland transplantation on July 31, 1923, writes thus:

"I. A very marked increase in my physical vigor. Before the transplantation I tired easily and recovered slowly from bodily fatigue. This has practically all disappeared. I apparently can do as much as I could thirty years ago, and even if I do get tired I rest for fifteen minutes and it puts me right again.

"II. A marked increase in my mental activities. My mind seems now more active than it was at thirty-five years. It has much more to work on now, as I have had much valuable experience in the past thirty years. I seem to be able to grasp and solve problems more readily than I could as a young man. It was the diminishing mental and physical vigor which impelled me to take the transplantation. I felt I was getting to be an old man. The feeling has disappeared and I am always ready for mental or physical work.

"III. Gradually increasing sexual power. While this was never entirely lost, I felt that it was gradually diminishing. It is just as surely gradually increasing since the transplantation.

"IV. I have been practically bald for many years. The hair is beginning to come in on the bald spot and of its natural color.

"V. As a young man I used to enjoy cold baths, but for a number of years I have not been able to take these as I did not get the proper reaction. I have gone back to cold baths and get a fine reaction. . . ."

Case 6. Dr. F., a medical editor, writes the following letter after the operation of gland transplantation performed in September, 1923:

"For many months prior to the operation, I was beginning to lose my usual vim and vitality. I did not have the energy to do my work and really 'did not care whether school kept or not.' I was beginning to realize that a condition simulating physical and mental hebetude was slowly tightening its grasp upon me. Since the operation I am feeling more like I used to in the days gone by.

"My circulation has improved, my complexion is again ruddy, and I am feeling as physically fit again as I did ten years ago."

Case 7. Dr. G., aged 40 years, visiting surgeon to one of the State Hospitals and attending surgeon to several general hospitals, was suffering with incomplete impotence of five years' duration. He has made no report following the transplantation.

Case 8. Dr. H., aged 56 years, an American, married and the father of two children, was operated on for impotence on March 28, 1923. He complained of great mental and nerve depression and severe attacks of dizziness during the previous twelve months. The laboratory findings were negative. An abstract of a letter written by this patient on March 8, 1924, reads thus: "I want to say that I feel in every way that I am a much more satisfactorily fuunctioning individual than before the operation."

Case 9. Dr. I., aged 59, a member of the American Medical Association and on the staff of a large hospital, complained of complete impotence, marked exhaustion, insomnia and sciatic neuritis.

This patient had had a Steinach operation and a previous transplantation by a western surgeon without results. A transplantation was performed on this man on June 17, 1924. The gland within five days sloughed away and no further transplantation was performed.

The next five cases include three wives and two sisters of physicians.

Case 10. Mrs. J., aged 46, American, the wife of a retired physician (Harvard graduate), following ovariotomy performed five years previously, entered upon an aggravated menopause. She developed mental symptoms, frigidity, claustraphobia, marked physical weakness, aggravated insomnia. gastric and intestinal atony and consequent indigestion. With the development of these symptoms the husband placed his wife on increasing doses of ovary, and, on large doses, some improvement in the general condition was noted, sufficient to make the husband feel that gland transplantation might give complete relief. This operation was performed on August 31, 1923. A point of particular interest in this case is that it shows that the results were in no way due to any psychic effect. At the time of the operation, feeling that this patient was entirely lacking in ovarian secretion on account of her ovariotomy, it seemed well to support the gland tissue by the continuance of ovarian secretion given hypodermically, I therefore advised the doctor to continue this ovarian secretion, even doubling the dose. This was done, and forty-eight hours after the transplantation the hot flashes and claustraphobia had disappeared. The patient then stated that she did not see how she could ever have experienced the claustraphobia. This almost immediate effect which is seen in so many cases is probably due to a certain amount of free secretion being absorbed immediately after the transplantation. These immediate effects are often seen whether the gland undergoes later necrosis and sloughs out or remains. The week following the transplantation the patient came to the office for a dressing and stated that she was afraid the transplant was not a "take," as she was again suffering from the same symptoms she had had before the operation. She was laid on the table and when the dressing was removed the gland had worked out and was found to be adherent to the gauze. In answer to the patient's query as to whether the gland was a "take" or a "non-take," I informed her that without question it was a "take." Stepping into the next room, I explained to the husband that the gland had sloughed out and that he should prepare his wife for another transplantation. The thought I had in mind when I told the patient that the operation was a success was that if there was anything in her psychic attitude that would influence her symptoms I did not want to destroy it. The husband expressed his appreciation of the way in which I had handled the matter. He said that he believed the shock of knowing that there had been a "non-take" would have influenced his wife against further transplantation, as well as upsetting her mental condition. Within twenty-four hours after the patient left the office all the symptoms had returned in their old aggravated form, and this in spite of the fact that the ovarian extract was being given in double the dosage that it had been given previously, and regardless of the fact that the patient felt that the transplantation had been a success.

A second and successful transplantation was made on November 9, 1923. The effects of this transplantation lasted until March 25, 1925, when another successful transplantation was made. The relief from this operation lasted until the following October. A fourth transplantation was made on October 6, which gave relief which continued until May, 1924. A fifth transplantation was performed on May 24, 1925, which has been successful in maintaining an improvement in the patient's condition.

It is of course evident that as there are no ovaries present the transplanted gland must supply all the ovarian hormone that the patient's organism called for and that the transplanted gland supplied this for a period of about six months, an unusually short period of time, but not short considering the absence of normal ovarian secretion. This is an instructive case from many angles.

Case 11. Mrs. K., aged 46, married, the wife of a California physician specializing in pediatrics, the mother of one son, gave an unusual menstrual history. She began menstruating at the age of 22 years, the flow lasting only half a day. She frequently suffered from a partial amenorrhea extending over a period of from a few months to several years, until, at the age of thirty-five, she was operated upon, having one ovary completely and the other partially excised. The operation seemed to make little difference in her menstrual conditions. Three years before transplantation was done menstruation had disappeared entirely. On Jan. 22, 1925, an ovary was transplanted, but as there were no apparent results, within three weeks another transplantation was done, on February 17th. Following this operation the patient began to menstruate normally. She stated that it was the first normal menstruation she had ever experienced, the flow lasting four days. The patient continued to menstruate regularly and normally until Sept. 9, 1925, when she stated that menopausal symptoms had reappeared. Two ovaries were then implanted, after which all the patient's menopause symptoms cleared up. The vasomotor disturbances (hot flashes) disappeared, and there was a reduction of about 18 pounds in weight.

The above cases have been selected for report because the technical training of the patients renders their statements more convincing than those of lay patients. The small number of cases included, of course, renders any valid statistical deductions impossible. Of the total 305 transplantations made, many patients have shown results infinitely more singular than those above quoted. These cases will be reported at a later date.

In 1920, when my meditations and reflections on this subject caused me to test gland transplantation, I did so with my eyes open. I knew the profession usually pronounces against novelty. I knew failure would invite ridicule rather than criticism. In consequence, for several years I nursed my theories in loneliness and my results in silence until I was invited to read a paper on the subject before the Medical Editors' Association during the 1923 Congress of Surgeons in Chicago. A laborer's work is often more interesting than the laborer. The gracious enthusiasm and courtly criticism of that society of learned and polished minds, encouraged me to further research—to come out of my trench as it were into "no man's land"—to stand by my beliefs and avoid defrauding of due esteem, results that, in some instances, are to say the least, singular and remarkable.

BIBLIOGRAPHY

1. Hunt, H. L.: Experiences in testicle transplantation. This Journal, 1922, 6, 652-654 (Sept.).
   Further experiences in gland transplantation. New York State J. M., 1923, 23, 488.

2. Robinson, Wm. J.: The menopause and change of life. Woman's critical age. New York, 1923, Critic and Guide Co.

3. Delafield & Prudden: Text-book on pathology. N. Y., 1925, 13 Ed., Wm. Wood & Company.

4. Tanenbaum, J. L.: Pathology and mechanism of prostatic hypertrophy. J. Urol., 1922, 8, 431.

5. Fischer, A. W.: Zur patholigische Anatomie Prostathypertrophie. Deutsche Ztschr. für. Chir., 1921, p. 162.

6. Thorek, Max.: The human testes. Phila., 1924, J. B. Lippincott & Co.

THE PANCREAS AND TUBERCULOSIS

LOUISE G. ROBINOVITCH, B. ès L., M. D.
GEO. W. STILES, JR., B.S., Ph.D., M. D., and C. F. PAYNE
From the Chemical Laboratories of the Colorado State
School of Mines,

GOLDEN, COLORADO

During the years 1921-1925, while autopsying guinea pigs that had died of tuberculosis, the senior author noticed that the pancreas remained free of the diseace, macroscopically, even when the lungs, liver and spleen were severely degenerated by the tubercle bacilli; occasionally there seemed to be an enlarged lymphatic gland along the margin of the pancreas, but no serious tuberculous lesion seemed to exist in the glandular tissue itself.' All these autopsies, over two hundred in number, were made in the U. S. Bureau of Animal Industry, Denver, Colorado. Dr. Robinovitch asked Dr. Stiles to add his observation to hers when her tuberculous guinea pigs were being autopsied. Dr. Stiles checked up these findings and failed to observe any tuberculous lesions of the pancreas of the guinea pigs that had died of tuberculosis. Dr. Robinovitch then asked the Inspector in charge of Field Work, Dr. W. E. Howe, U. S. Bureau of Animal Industry, Denver, Colorado, to make inquiry at the U. S. Bureau of Animal Industry, Washington, D. C., and at the Denver Division of Meat Inspection, Denver, regarding tuberculosis of the pancreas in cattle and in hogs. The reply from Washington reached here June 15, 1925. Its substance was as follows:

"It is not recalled that tuberculosis of the pancreas has been reported on M. I. Form 112-F, although it is possible that such infections have been recorded by post-mortem inspections."

The substance of the letter from Dr. Payne, dated May 14, 1925, was:

". . . . . you are advised that we have caused careful examination to be made of all pancreatic glands from hogs and cattle carcasses retained for tuberculosis at the station for a period of thirty days, and failed to find a single instance where

the glands were affected with tuberculosis. This report is based in all cases on the usual macroscopic examination.

"During this test we examined the pancreatic glands from forty-nine cattle and two thousand one hundred and twenty-four hogs."

To make sure that no gross mistake has crept into her observations, Dr. Robinovitch made a further appeal to Dr. Howe for additional observations by Dr. Payne. The appended extract from a letter from Dr. Payne, dated July 21, 1925, again confirmed Dr. Robinovitch's findings:

". . . . we have examined during the past thirty days the pancreatic glands from all hogs and beef carcasses retained on account of tuberculosis, and failed to find any that were affected with tuberculosis. This report is based on the examination of the pancreatic glands macroscopically.

"During this period we examined the pancreatic glands from one hundred and thirty-one cattle and one thousand six hundred and forty-three hogs which had been retained on account of tuberculosis."

It is evident, therefore, that tuberculosis of the pancreas is a rare occurrence in animals.

TUBERCULOSIS OF THE PANCREAS IN HUMAN BEINGS

VanValzah (1) reported one case of tuberculosis of the pancreas out of two hundred autopsies on tuberculous subjects. A comprehensive review of the literature on the subject is given, showing the marked rarity of tuberculosis of the pancreas in human beings.

It seems further, then, that tuberculosis of the pancreas is a rare disease in human beings as well as in animals.

May 18, 1923, an experimental study was published (2) dealing with the chemical effect of lipase and insulin on the waxy coating of the tubercle bacillus; the lipase with the accompanying small percentage of insulin was obtained from the pancreas. A more detailed study of the chemical effect of lipase and the accompanying small percentage of insulin was published by Robinovitch and Stiles (3), dealing with the chemical effect of lipase and insulin on the waxy coating of the tubercle bacillus. It was shown by numerous experiments in that study that lipase or steapsin (and to some extent insulin) contained in the pan-

creas act as hydrolyzing agents of fat and wax; and that the waxy coating of the tubercle bacillus is readily hydrolyzed by the lipase of the pancreas. This destructive effect on the tubercle bacillus, caused by the lipase of the pancreas (and to some extent by the insulin) explains the marked immunity of the pancreas against infection with tuberculosis. It was stated in that study that the results of tests with lipase and insulin on tuberculous animals would be reported when a sufficiently large number of cases are collected.

CONCLUSIONS

1. The defensive agent of the pancreas against the tubercle bacillus in animals and in man has been demonstrated in the above studies to consist essentially of the lipase or steapsin (and to some extent of the insulin) in the pancreas.

2. The lipase or steapsin contained in the pancreas or in any part of the body is a defensive agent, in animals and in man, against the tubercle bacillus.

3. It is possible that persons contracting tuberculosis are subject to a deficiency of lipase in their systems.

Dr. Robinovitch takes great pleasure in expressing her indebtedness to President M. F. Coolbaugh, of the School of Mines, for having given her facilities at the School to continue her work. She also expresses her deep obligation to Dr. W. E. Howe for his great help in this work.

BIBLIOGRAPHY

1. VanValzah, S. L.: Am. Rev. Tubercul. (Balt.), 1924, 9, 409.
2. Robinovitch, Louise G.: A chemical basis for the treatment of tuberculosis. A preliminary statement of research work from the chemical laboratories of the Colorado State School of Mines, Golden, Colo., issued by the School of Mines; presented at the Fifth Joint Meeting of the El Paso County Sanatorium Ass., Phipps Sanitarium, May 26, 1923, Denver. Second issue of the publication by the School of Mines, May 30, 1923.
3. Robinovitch, Louise G., & Stiles, G. W.: A chemical basis for the treatment of tuberculosis. Experiments on the action of steapsin and insulin on tubercle bacilli. Am. Rev. Tubercul. (Balt.), 1924, 9, No. 6 (Aug.).

THE NUMBER OF ISLETS OF LANGERHANS IN THE PANCREAS OF THE ALBINO RAT

MILTON D. OVERHOLSER

Department of Anatomy, University of Missouri

The purpose of this work was to determine the relation of age to the total number of islets of Langerhans in the pancreas of the albino rat.

Several investigators have made counts of the islets in pancreases of various animals in studying the process by which normal regulation of the islet content of the pancreas is maintained. Prior to 1911 our knowledge of the number of the islets was based upon estimations from partial counts by the section method. Since it was impossible to examine and count the islets in a complete series of sections of the whole pancreas these studies produced only relative and computed numbers.

By this method Opie ('00) obtained a numerical statement of the relative abundance of the islets in different portions of the human pancreas. He counted the number in sections of 0.5 square centimeters from the enlarged duodenal portion or head, from the mid-portion or body and from the splenic end or tail. The average number of islets in such a section from the head, body and tail of ten normal organs was 18.3, 19.0 and 34.0 respectively. Squaring these numbers to obtain cubic units, he found the islets to be slightly less than three and a half times as numerous in the tail as elsewhere.

Dewitt ('06) carried out an extensive investigation on the morphology and histology of the islets by studying serial sections of injected and uninjected preparations of pancreas of man, cat, rabbit, guinea pig, frog and dove. She made no computed counts of the total number of islets, but gave only the average number of islets per square millimeter, the average volume of the islets, and the percent of islet tissue in the various pancreases studied.

The human pancreases studied by Dewitt included organs from a new born infant, a four year old child, and a normal adult. She stated that the average size in the adult was actually

greater than in either of the other cases, while in the four year old child it was greater than in the new born infant. Moreover, in the four year old child the proportion of islet to acinus tissue was much greater than in either of the others. She found the islets generally larger and more numerous in the central portion of the pancreas, especially in the dove, guinea pig and rat.

Bensley ('11) applied new methods of accurate enumeration to the islets of Langerhans in the pancreas of the guinea pig. He stained the pancreas by injecting solutions of neutral red and janus green in the aorta after the animal had been killed by bleeding. A lobule of the pancreas stained with neutral red and mounted in normal salt solution under a cover glass showed the islets stained an intense yellow red, while the rest of the pancreas was a faint rose tint; the janus green stain showed the islets deeply blue on a red background. By means of the neutral red method Bensley made actual total counts of the islets in sixty-five normal resting pancreases from guinea pigs. There was great variation in the total number, the counts ranging from 13,318 to 56,722.

Clark ('13) made counts of the islets in seven human pancreases by Bensley's neutral red method. Thin free hand slices were cut with a razor from different parts of the head, tail, and body. Pieces from each of these sections were mounted in Ringer's solution and the islets counted. From relative weights the total number and relative distribution of islets were calculated. The following table of his results is quoted for the purpose of comparing it with the figures obtained in the present investigation:

TABLE 1

Counts of Islands of Langerhans in the Normal Human Pancreas—Clark

Age in years	Body weight in lbs.	Sex	Estimated total number of islands in pancreas	Approx. no. of islands per gm. wt. of person	Weight of pancreas in gms.	Average no. per mg. of fresh pancreas
34	130	M	353,765	....	103.	......
24	140	M	1,760,000	27.7	87.	20.23
½	12.1	F	120,323	21.8	5.582	21.55
22	105	F	1,534,085	32.2	82.7	18.55
45	125	M	737,469	13.0	53.705	14.39
29	135	M	662,166	10.8	61.511	10.76
45	150	M	208,369	3.0	55.923	3.72

METHOD

In the present investigation, Bensley's neutral red method was used to stain the islets of Langerhans. The animal was anesthetized, the abdomen opened and the lower end of the aorta and inferior vena cava cut to secure thorough bleeding. Immediately after death the thorax was opened and a glass cannula inserted and tied in the aorta. The cannula was then connected by a rubber tube with an elevated Wolff bottle and, by means of gravity, neutral red, one part in 15,000 of isotonic salt solution, was injected. The cut ends of the aorta and inferior vena cava were clamped off to prevent escape of the injection fluid. The pancreas took on a rose tint within a few minutes, and the injection was stopped after a sufficient depth of color was obtained. The time required to stain the pancreas sufficiently varied from fifteen to thirty minutes, and it was extremely important that the injection be stopped at the right time, otherwise overstaining or understaining resulted and the ·preparation had to be discarded.

In the case of the animals less than one week in age, the above procedure was changed somewhat. The head and one hind leg were cut off to produce free bleeding. A very fine glass cannula, supported by an adjustable stand and manipulated under the low power of the binocular dissecting scope, was required to cannulate the aorta. No attempt was made to clamp off the ends of the cut vessels as the leakage was comparatively slow and did not interfere with a good injection. It was necessary to allow the injection to run from one hour to an hour and a half to insure sufficient staining of the islets.

In removing the pancreas the stomach, intestine and spleen were also taken out en masse. The intestines were cut away with the exception of part of the duodenum and transverse colon which have a portion of the pancreas embedded in their mesenteries. The stomach was then emptied of its contents and the preparation pinned out in normal salt solution on a paraffin bottomed petri dish.

The pancreas was then divided into three major portions: (1) duodenal, that part on the right of a line following the portal vein from the junction of the splenic and superior mesenteric veins to the point at which it passes behind the first part

of the duodenum; (2) splenic, that part on the left of a line passing from the junction of the splenic and superior mesenteric veins along the left border of the omental portion of the pancreas; and (3) mid-portion, the rest of the pancreas between these two lines.

Each division was cut up into portions about five millimeters square and of the thickness of single lobules which were mounted in normal salt solution under a cover glass. Such preparations examined under the high power of the dissecting binocular showed the islets of Langerhans stained yellow red, while the rest of the pancreas showed a faint rose tint. The islets in each piece were then counted, a mechanical stage being used to prevent omission or overlapping of the fields. The pieces were collected from the slides as rapidly as the counts were completed and again placed in normal salt solution, the pieces belonging to the major divisions of the pancreas being kept separate. After the total count was completed the pieces were pressed lightly between layers of filter paper to remove excess salt solution and weighed.

The stain was not permanent and exclusion of oxygen from the preparation as occurred in the case of the mounted pieces hastened the reduction of the dye. The stain first disappeared from the acinus tissue, so that a certain amount of reduction was favorable, especially in slightly overstained pancreases, as it left the islets more sharply differentiated. The inevitable reduction of the dye, however, began to overtake the smaller islets in three to four hours, so the time for making the counts was limited. The pieces of pancreas were mounted as needed and it was usually possible to complete the count in the entire pancreas within three or four hours.

The chief sources of error in this method, as pointed out by Bensley, were due (1) to overstaining of the zymogen granules which obscured the smaller islets, (2) to the high refractive index of the zymogen granules making the pieces less transparent, and (3) to the error in comparative weighing, owing to different amounts of salt solution being abstracted from the pieces in different cases. The latter error might have been considerable if several workers had been preparing the material for

weighing, but in the hands of a single worker following a definite routine, the results should be fairly accurate.

The results obtained in forty-four animals are recorded. These animals may be classed as follows: (1) eleven whose exact ages were not known but ranged between ninety and one hundred and fifty days were from mixed litters obtained outside the laboratory; (2) twenty-three were from four litters raised in the laboratory and of ages ranging from two to eighty-five days; (3) eight were from seven litters raised in the laboratory and of ages ranging from one to forty-two days; (4) two from the Wistar Institute were eight hundred and sixty-four and nine hundred and one days old respectively.

PRESENTATION OF DATA

. Table 2 shows the data arranged according to a progressive increase in the body weights of the animals since the exact age of some was not known. The increase in body weight corresponds, of course, in a general way, with increase in age; therefore comparisons of the total number of islets with body weight or age can readily be made from this table.

GRAPH-1

Graph 1. Relation of number of islets to ages of animals; table 2.

Graph 1 shows the relation of the total number of islets to the ages of the animals. In plotting the results of the eleven animals whose ages were between ninety and one hundred and fifty days the mean age of one hundred and twenty days and the average of the total numbers were taken. The curve shows that during the first twenty days of life the number of islets rapidly increases and then maintains a maximum value for the next thirty days. From this point (fifty days) there begins a slight decrease which, however, apparently continues only for the next fifty or seventy-five days.

TABLE 2

Entire Data Arranged According to a Progressive Increase in the Weights of the Animals

Wt. in gms	Age in days	Sex	Wt. of pancreas in mgs.	Total no. of islets	No. of islets per mg. of pancreas	No. of islets per gm. body wt.	No. of islets per mg. in divisions of pancreas*		
							D	M	S
4	1	..	...	1,494	...	373	...	...	...
5	4	M	15	1,575	106	350	8	9	125
5	5	M	14	1,517	108	276	105	138	97
6	2	M	12	2,002	167	333	146	162	182
8	2	M	18	1,995	110	235	116	133	94
11	4	F	30	2,199	72	191	67	81	72
16	7	F	49	3,618	75	226	57	81	89
17	14	F	34	3,417	99	195	95	117	95
22	21	F	111	3,606	32	160	27	32	37
32	28	F	208	9,571	46	294	41	48	49
33	21	M	115	6,089	53	183	45	59	56
40	17	M	86	12,628	147	312	134	163	150
44	35	M	281	9,494	34	216	31	37	35
48	24	F	275	8,530	31	178	22	46	32
48	35	M	270	2,938	11	61	8	10	14
49	28	F	295	9,090	31	185	29	53	27
50	28	M	212	8,693	41	174	30	64	41
64	35	F	376	9,082	24	142	22	33	23
64	56	F	390	5,985	15	93	11	19	18
64	49	M	387	9,784	25	152	21	33	26
72	28	F	488	9,035	18	125	13	26	20
73	31	F	458	6,875	15	94	13	15	17
88	63	F	628	5,282	8	60	6	11	9
109	40	M	620	14,579	23	134	18	26	27
113	51	M	631	7,819	12	69	12	14	12
115	85	M	557	8,750	16	76	12	21	17
116	42	F	828	6,938	8	71	7	10	9
118	58	F	332	8,329	10	70	7	10	12
142	...	M	697	5,727	8	40	8	8	8
144	80	M	677	11,126	16	77	11	13	21
154	...	F	613	4,314	7	28	7	9	7
164	70	M	599	6,461	11	39	7	12	12
166	...	F	670	10,048	15	60	14	22	13
169	65	M	859	5,962	7	35	7	7	7
173	...	M	572	6,009	10	35	9	8	13
175	...	M	485	8,684	18	50	14	22	19
184	...	M	627	4,915	8	27	5	9	9
189	...	M	639	6,636	10	35	10	13	10
198	...	M	518	5,794	11	29	6	14	14
198	...	F	917	6,422	7	32	6	6	8
216	...	M	742	4,548	6	21	4	8	7
266	864	M	779	7,654	10	29	9	10	10
316	...	M	1,053	5,024	5	16	3	4	6
364	901	M	949	4,595	5	13	4	5	5

* D—Duodenal portion. M—Mid-portion. S—Splenic portion.

GRAPH—2

Graph 2. Relation of number of islets to body weights of animals; table 2.

Graph 2 shows the relation of the number of islets to the body weights of the animals. The rapid increase in the number of islets up to the twenty-five or thirty gram animal corresponding with the first twenty days of life is clearly shown. The maximum is then maintained up to seventy-five or one hundred grams with the decrease then occurring up to the one hundred and eighty or two hundred gram animal.

GRAPH-3

Graph 3. Relation of number of islets per gram body weight to body weights of animals; table 2.

Graph 3 shows the relation of the number of islets per gram body weight to the weights of the animals. There is a rapid decrease in the number with increase in body weight up to the one hundred and twenty gram animal. From this point a slow decrease occurs with advancing body weight.

GRAPH - 4

Graph 4. Relation of number of islets per milligram of pancreas to body weights of animals; table 2.

Graph 4 shows the relation of the number of islets per milligram of pancreas to the body weights of the animals. The number rapidly decreases up to the sixty gram animal, a very slow fall then continuing with advancing body weight.

The above curves show that although the islets increase in number to a certain extent in the growing pancreas, the number per milligram of pancreas and per gram body weight decreases with the growth of the animal.

The rapid decrease in the number of islets per milligram of pancreas occurring up to the sixty gram animal, followed by a slow decrease with advancing body weight, indicates that in the growing pancreas for the first forty or fifty days there is a much more rapid increase in acinus tissue than in the formation of new islets. Since the period of the maximum number of islets ends at about this age (fifty days) the continued slow fall in the number per milligram of pancreas is due both to the slight decrease in the total number of islets and the slower increase of acinus tissue during the remaining growth period of the pancreas.

It is realized that mere total numbers of islets cannot be an exact guide to the relative amount of islet tissue present in the pancreas at any time during the life of the animal. The size of the islets is highly variable and without doubt an increase or decrease in the absolute amount of islet tissue may occur without a corresponding increase or decrease in total number. It should be possible to devise a method whereby the absolute amount of islet tissue in the pancreas can be determined for the entire life cycle of the animal. Meanwhile the above results on total numbers may be of some use and interest. They compare favorably with Clark's results in the human pancreas. By referring to his table, quoted above, it will be seen that he obtained a low count in the one-half year old child, a very high count in two young adults twenty-two and twenty-four years old, and a lower count in each of four adults of an average age of thirty-eight years.

Figures 1A, 1B and 1C show the variability of the size of the islets and the high number per unit of pancreas occurring in an animal two days old. Figures 2A, 2B and 2C show that in a

thirty-five day animal the number of islets per unit of pancreas is much lower than in the two day animal. The total number of islets, however, is much higher in the former animal than in the latter.

1A

1B

1C

Figures 1A, 1B, 1C.—Pancreas of a 2-day animal. Letters A, B, C refer to duodenal, middle and splenic portions of the pancreas, respectively.

All drawings were made with a camera lucida from preparations similar to those in which the total counts of the islets were made. Acinus tissue, stippled; islet tissue, solid black. Magnification X 18.

SUMMARY

Using Bensley's method of staining the islets by injecting neutral red in the aorta, counts of the total number of islets in

the pancreases of forty-four albino rats, ranging in ages from one to nine hundred and one days, were made. The results may be grouped according to the following age classes of the animals.

The average number of islets per milligram of pancreas and per gram body weight for each class and for all of the counts was as shown in the following table.

Figures 2A, 2B, 2C.—Pancreas of a 35-day animal.

The average number of islets per milligram in the major divisions of the pancreas for each class and for all of the counts was as follows.

CONCLUSIONS

The absolute number of islets in the pancreas of the albino rat is variable yet, in a general way, the number markedly in-

creases during the first 20 days of life, then reaches and maintains a maximum value for the next 30 days. From this point there begins a slight decrease with advancing age, apparently reaching a level in animals 90 to 150 days old which is maintained in animals 880 days of age.

TABLE 3

Class	Age in days	No. of animals	Range in total numbers	Average of total numbers
1	1 to 21	11	1,494 to 12,628	3,650
2	24 to 51	13	2,938 to 14,579	8,650
3	56 to 85	7	5,282 to 11,126	7,400
4	Between 90 and 150	11	4,314 to 10,048	6,200
5	864 and 901	2	4,595 and 7,654	6,100

The number of islets per milligram of pancreas is highest at birth, there being a very rapid decrease during the first 40 or 50 days of life, and then a much slower fall with increase in age.

TABLE 4

Class	1	2	3	4	5	Average
Average number of islets per mg. of pancreas..........	97	25	12	10	7 5	34
Average number of islets per gm. body weight..............	258	146	64	34	21	127

The number of islets per gram body weight decreases with the growth of the animal; the decrease is at first rapid and then slow; the first 60 or 70 days of growth is the period of the rapid decrease.

TABLE 5

Class	Duodenal portion	Mid portion	Splenic portion
1	88	107	97
2	21	32	25
3	9	13	14
4	8	11	10
5	6	7	7
Average.............	29	38	34

The mid-portion of the pancreas as delimited in this investigation ranks highest in islet content, the splenic portion being second and the duodenal portion third.

BIBLIOGRAPHY

Bensley, R. R.: 1911. Studies on the pancreas of the guinea pig. Am. J. Anat. (Phila.), **12**, 297-387.

Clark, Elbert: 1913. The number of islands of Langerhans in the human pancreas. Anat. Anz. (Jena), **43**, 81-93.

Dewitt, Lydia M.: 1906. Morphology and physiology of areas of Langerhans in some vertebrates. J. Exper. M. (Balt.), **8**, 193-238.

Opie, E. L.: 1900. On the histology of the islands of Langerhans of the pancreas. Johns Hopkins Hosp. Bull. (Balt.), **11**, 205-209.

PRELIMINARY NOTE ON THE MATERNAL BEHAVIOR OF RATS LIVING IN PARABIOSIS

CALVIN P. STONE

Department of Psychology

STANFORD UNIVERSITY

Experimental evidence accumulating during the past few years definitely connects the liberation of internal secretions from the ovary with the phenomenon of sexual receptivity in female rats (Lipschütz '24). A striking illustration of this causal relationship was recently given by Allen ('24) when he demonstrated that sexual receptivity may be brought about in premature females or females from which the ovaries have been removed by the injection of fluids taken from the mature Graafian follicles of swine. Familiarity with this evidence has led the author to raise the question as to whether maternal behavior is similarly conditioned by hormones liberated at or near the time of parturition. Experimental observations on the rat would seem to show that maternal behavior is not aroused by any known factors of the external environment that are equally potent for non-pregnant and virgin females, but that it is in some way conditioned by physiological factors attendant upon pregnancy, parturition, and nursing of young. Although non-pregnant multipari and virgins, as well, sometimes bring together nesting materials when these are available, they do not work at the task with the industry ordinarily displayed by the female that has just delivered a litter. Neither are they solicitous for new-born young in their cages when the latter belong to other females. Such observations and others of similar nature would seem to indicate that maternal behavior is activated in part, at least, in females by factors originating within their own bodies and that substitutes for these factors cannot be supplied to the virgin by manipulating stimuli from the external environment.

In the preliminary attempts to bring this problem to experimental test a technique involving the making of a special type of "Siamese twins" was employed. The bodies of young

females were united by joining the integument of one with that of the other. Through this union of skin, substances in the circulatory system of one animal may diffuse into the body of the other, and, theoretically, to continue the line of reasoning, a maternal hormone from one female might be transferred to the other with which she lived in parabiosis and, retaining its potency, might activate maternal behavior in the latter.

Other experimenters have demonstrated the possibility of effecting an interchange of substances between the blood stream of one animal and that of another with which it is joined. Sauerbruch and Heyde ('08) found that indelible ink injected into one of two rabbits with bodies joined will diffuse into the other as early as the fourth or fifth day after they are united. They concluded also that the kidneys of one animal of the pair may be removed without causing its death since the kidneys of the other will serve the needs of both. Furthermore, they found that the internal secretion of the pancreas may pass from one dog to another from which the pancreas has been removed. Working with rats, Morpurgo ('08) showed the feasibility of joining animals of the same and animals of the opposite sex. The reproductive tracts of a male and female rat joined for several months prior to autopsy were found as well developed as those of animals living under normal conditions. Yatsu ('21) also demonstrated that the testes of a male are not affected by union with a normal or spayed female and that the normal female of such a pair is fertile. Females united with castrated males, however, were said to be unfertile.

OPERATIVE TECHNIQUE

Two animals, anaesthetized simultaneously, were put side by side on the operating table and the skin of the juxtaposed sides, from which the hair in the operative field had been removed, was thoroughly saturated with a ten per cent solution of iodine. Then an incision one inch long was made in the skin of the adjacent sides midway between the shoulder and the hip. Next, small margins of skin, both above and below the incision, were cut away so that an elliptical portion of the lateral abdominal wall was exposed. The short and long diameters of this ellipse were one-half and one inch, respectively. Finally the

animals were brought together and the adjacent edges of skin sutured with strong linen thread.*

To prevent or minimize tension on the sutures while the skin was uniting, a band of adhesive tape was wrapped around the bodies of the animals. We hoped that this band could be removed after the wound had completely healed, but such was not the case. The animals never willingly accepted the necessity of idling together or moving simultaneously in the same direction, hence it was necessary to keep them banded at all times. Soiled bands were removed as occasion demanded.

Very little difficulty was encountered in securing skin unions between the two animals. The source of greatest difficulty, however, was that of keeping the animals joined after the union was formed or in keeping them in a healthy condition. In some instances the animals gnawed through their bandages during the night and, by tugging and twisting, either tore the newly joined skin or irritated it to such an extent that separation was inevitable. In other cases, for reasons not known, one of the animals gradually became inactive, ceased to eat, and eventually died. Similar results were reported by Morpurgo ('08). Although several pairs of animals joined by skin unions have been kept alive and healthy for a few weeks, and three pairs for over two months, only one pair was maintained sufficiently long to permit of breeding and subsequent observations on maternal behavior.

MATERNAL BEHAVIOR OF PARABIOTIC RATS

On March 1, 1924, the bodies of two females of the same litter were joined. They were approximately three months of age, and both were sexually mature. For convenience of description, the animal on the left will be designated by the letter L, and the animal on the right by the letter R. Female L was slightly smaller than R when joined, and their subsequent growth never altered this weight relationship. Examination of vaginal smears (Long and Evans, '22), at irregular intervals after the operation showed that both animals had oestrual cycles. On April 29, Female R was found in "heat" and was bred. Although the male sometimes mounted and attempted

copulation with L, the latter was totally unreceptive. Her oestrual cycles were independent of those of R.

Animal R carried the young through the usual period of gestation and delivered a litter of five living young. Throughout the time of parturition the experimenter was present and, for approximately one and one-half hours afterward, observed the behavior of both animals. Female R removed the foetal membranes from each young as it was delivered and cleansed it of the liquor amnii. During the first hour, she picked up some of them in her mouth as if attempting to carry them about the cage. It would seem that she was trying to assemble them for the purpose of making a nest. These attempts were frustrated by animal L, which did not participate in the act of cleansing the young and, through inactivity or contrary impulses, greatly curtailed R's movements about the cage. No maternal responses whatever were displayed by L during this period of observation.

About five hours later, the females were again under observation for approximately one hour. At this time, R took the young from the experimenter's hand into her mouth and carried them from the front to the rear of the cage where they were deposited on the floor. Sometimes she did not at once succeed in reaching the rear of the cage, for it was always necessary to drag L with her. The latter usually resisted the movements. Inspection of the abdomen of the young for milk, which is visible through the belly wall if the young have recently nursed, led to the conclusion that none of the five had suckled All of them died within the first thirty-six hours after birth. From time to time during the first two or three days after parturition female R was observed picking up bits of paper scattered about the cage and attempting to pull them together to form a nest. Similar behavior has been observed in other mothers that have lost their young. She took pieces of paper from the experimenter's hand as they were held out to her at the entrance of the cage and attempted to carry them to the rear. Animal L did not pick up paper for the nest and would not accept paper from the experimenter's hand.

About three weeks after the female had lost her litter, a male was put into the cage of the pair in the hope that one or the other of the females might again be impregnated. On July

10, Animal R delivered her second litter (nine young). The experimenter was not present at the time of parturition, but found the young a few hours later. The young were assembled into one corner of the cage and the pair of adults was hovering over them.

In order to elicit unequivocal signs of maternal behavior the nest materials and young were scattered. Soon afterward female R began to pick them up and to carry them back to the nest. She assembled them four times during the first day. As a rule she began to gather them immediately after they were scattered about. On the second night the experimenter observed her sweeping shavings into a heap in one corner of the cage where the young were huddled together. Similar behavior was repeated several times while observations were continued during the first ten days. Female L did not participate in the work of moving nest materials, take the young into her mouth, pick up paper, or sweep shavings from the floor. Animal R dominated L in her movements about the cage and because of her superior strength was able to move the latter about in whatever direction she attempted to go. Perhaps less resistance was now offered to her movements than on the occasion of the first litter; at any rate, the mother succeeded in going about the cage almost at will. Sauerbruch and Heyde ('08) seemed to think that their animals gradually learned to move about with less and less conflict.

Inspection of the young for evidence of nursing during the first and second day showed that they were receiving very little if any milk from the mother. Between the second and third days all but one of the young died. In order that we might be assured of the opportunity of observing the females with young over a considerable period of time, two young animals, four days older than R's litter, were added to the nest. They were very vigorous sucklers and secured enough milk to sustain them until the age of weaning. On the evening of the tenth day a huge mass of paper and shavings that female R had brought together was scattered about the cage in order to test her inclination and ability to bring them together as in the early days after parturition. She gathered all the materials into one corner of the

cage and placed her young upon them as in similar tests given earlier.

On December 6 the ovaries of female L were removed. This was done for the purpose of ascertaining whether an ovarian hormone from R would pass over to L and bring about typical oestrual cycles. No evidence of the latter was observed after the operation. Within the first month the vaginal orifice began to close and at the end of the second month was almost completely obliterated. Thereafter only a pin point opening remained.

In February, 1925, female R again conceived and bore a litter (five young). This litter was first observed in the morning, and had probably been born some six hours earlier. The young were rather loosely scattered about the cage and only a small amount of paper had been brought together in one corner of the cage. At this time female R took the young into her mouth from the hand of the experimenter and deposited them on the side of the cage. Later in the same day she again gathered the young together after they had been scattered about. During the first evening all of the shavings in the cage were brought together to form a nest and in it the young were found on the following morning. An examination of each individual revealed milk in the abdomens of only three. The others were now less active than those that had nursed and were not making any effort to secure milk. During the second day the young that had not nursed were removed from the nest and three vigorous young from a litter one day older were substituted for them. Observations of maternal behavior were made again on this day. Female R always seemed ready to take the young or nest materials into her mouth and carry them back to the rear of the cage, but L did not do this at any time while under observation. And since observations were made again repeatedly during the the first ten days, both at night and during the day with similar results, it is assumed that she did not co-operate in the care of the young at any time.

During the first twenty-four hours after parturition, a rat usually becomes receptive to the male (Donaldson, '24). Anticipating the possibility of signs of the oestrus in female L, resulting from a transference of ovarian hormone from R after parturition, the pudenda of L were carefully inspected daily

for two weeks after the last litter was delivered. No change in the size of the pin-point opening of the vagina was noted. On the third day after parturition a small probe was inserted into the vagina to obtain a sample of the mucosa for smear examination. The cells of the smear were characteristic of the dioestrous interval.

Although the young nursed during a period of approximately four weeks they were suckled only by female R. On this, as one previous occasions, the nipples of L did not enlarge and no evidence of secretion of milk was obtained.

DIFFUSION OF TRYPAN BLUE

To ascertain the readiness with which fluids from one female might pass over to the other through the skin union we resorted to a test involving the injection of a vital dye into the normal female. Soon after the last litter had been weaned, 2 cc. of a saline solution of trypan blue was injected intraperitoneally into female R. The time of the injection was 9:45 A M. At 11 o'clock the blue coloration had become apparent at the nostrils and hairless regions of the feet of female L.[*] At 12 o'clock some coloration could be detected in the skin of L when she was put beside a control for comparison. Color of deeper hue was then observable in the skin of R. After 24 hours the whole skin of both animals was of a pale bluish tint. That of R was of deeper due than L. At the end of 48 hours the hue of both had become still deeper, but had not equalized Thereafter no additional change could be detected.

By way of ascertaining the amount of coloration in L at the end of 48 hours she was compared with other animals into which different quantities of the original solution had been injected at the same time R received 2 cc. The coloration of L at its highest point approximated that of a female that had received 0.5 cc. of the solution. Naturally it is impossible to state whether hormonal substances from the ovaries of R reached L, since, without the actual hormone at hand, no method of making the test similar to that of the trypan blue could be followed. It can be said with reasonable certainty, however, that conditions were favorable for their diffusion from one to the other of the females.

---

[*]Observations made independently by two observers

NECROPSY

Female L died after the animals had been united a few days over one year and seven months. Female R was anesthetized soon after the death of L was noted and the reproductive tracts of both animals examined. That of R was found to be in a healthy condition so far as external appearance served as a basis for judgment. The uterus and the uterine tubes were well developed and compared favorably in size with those of a normal adult female. The tract of L presented the appearance commonly following ovariectomy. The tubes had shrunken and the uterus was infantile in size. Neither tract was examined histologically.

CONCLUDING REMARKS

Although this study has not been carried sufficiently far, up to the present time, to warrant conclusions of a general nature, it would seem to have the special value of illustrating the possibilities of the "method of parabiosis" as an approach to the study of internal factors underlying maternal behavior. More intensive studies of females maintained in parabiosis and tested along lines similar to those described in the foregoing case history will probably throw some light on the question as to whether an internal secretion is responsible for the activation of maternal behavior in rats. For this reason it seemed desirable to bring the case to the attention of others interested in the study of maternal behavior in the hope that further studies of a similar nature might be stimulated.

BIBLIOGRAPHY

Allen, E., & Doisy, E. A.: The induction of the ovarian hormone in immature females by injection of the ovarian follicular hormone. Am. J. Physiol. (Balt.), 1924, 69, 577-588.

Lipschütz, Alexander: The internal secretions of the sex glands. Balt., 1924. Williams & Wilkins Co.

Diagstedt, L. R., & Cooper, Ethel P.: Parabiosis in the study of deficiency diseases. Am. J. Physiol. (Balt.), 1923, 67, 48-56.

Long, J. A., & Evans, H. M.: The oestrous cycle in the rat and its associated phenomena. Experimental studies in the physiological anatomy of reproduction. Memoirs of the Univ. of Calif. (Berkeley), Vol. 6.

Morpurgo. B.. über Parabiose von Säugetieren verschiedenen Geschlechts. Münschen. med. Wchnschr., 1908, 55, 153-156.

Sauerbruch, F., '& Heyde: Über Parabiose künstlich vereinigter Warmblüter. Münschen. med. Wchnschr., 1908, 55, 153-156.

Schmidt. Geo.: Weitere Paraboisestudien. Münschen. med. Wchnschr., 1920, 57, 1491-1492.

EXPERIMENTS ON LIVER TRANSPLANTATION

THEODORE KOPPÁNYI and HSI CHUN CHANG
From the Hull Physiological Laboratory of the University of Chicago

In reviewing the literature several publications were found dealing with the regeneration of liver tissue in different vertebrates. The authors (Griffini, 1884; v. Meister, 1891; Petrone, 1884; Ponfick, 1894; Tizzoni, 1883; Ribbert, 1904) as a rule obtained real regeneration of the hepatic cells, sometimes without any scar tissue formation. Encouraged by these reports, we carried out a series of experiments with transplantation of liver fragments in the bullfrog, albino rat and rabbit.

Autoplastic transplantations were carried out in the bullfrog (Rana catesbiana). One-third of the whole liver was cut off, divided into five approximately equal pieces and transplanted into the dorsal lymph sac, and into the peritoneal cavity. A month later the animals were killed and the grafts examined.

The grafts in the peritoneal cavity were resorbed without exception. The grafts in the dorsal lymph sac, however, revealed macroscopically normal appearance, retaining their original color. The histological examination showed slight necrosis in the center of the graft. At the periphery, however, and extending part way to the center of the graft, there was active proliferation of liver tissue with numerous mitotic figures. These proliferating cells were arranged in the form of tubes. Such tube formation has also been observed by other investigators who studied the regeneration of the hepatic tissue. The graft was abundantly vascularized and pigment inclusions were almost everywhere present in it.

Homoioplastic transplantations were carried out in the albino rat. Small fragments of liver tissue were transplanted, as a rule, into the peritoneal cavity. The grafts were examined one, two, three, and four weeks after the transplantation. One week after the grafting the transplanted liver fragments contained some living parenchymatous tissue, but on the whole they were undergoing degeneration. At the two, three, and four week stages no living parenchymatous tissue could be detected

in the grafts. Some of these transplants had established connections with the omentum and were surrounded by proliferating connective tissue. Prof. A. Maximow kindly aided us in the interpretation of the histological preparations.

As a further experiment, a thin small piece of rabbit liver was transplanted into the anterior eye-chamber of another rabbit. At the present writing, three and a half months after the transplantation, macroscopically the graft is still visible, but apparently it has been replaced by connective tissue. The keratomicroscopical examination by Dr. H. Gradle, one month after the transplantation, revealed that the graft with an exudate in its center was adherent to the iris and cornea and was supplied by blood vessels. At the same time, a pannus of the cornea was observed.

It is concluded that the frog's liver can be transplanted entirely successfully so far as determined by anatomical criteria and an investigation of the physiological activity of the transplants is contemplated. At present the attempts to transplant the mammalian liver must be considered as failures.

BIBLIOGRAPHY

Griffini.   1884, Arch. ital de biol. (Pisa), 5.
v. Meister   1891, Zentralbl. f. allg. Path., 8.
Petrone.   Arch. ital de biol (Pisa), 5.
Ponfick: Med. Zentralbl, 32.
Ribbert: 1904. Arch f. Entwcklngsmechn. d. Organ. (Berl.), 18, 267.
Tizzoni   1883 Accad Reale d Lincei, 280.

Abstract Department

Epincphrin anhydremia and its relation to the emergency function of the adrenals. Barbour (H. G.) & Hamilton (W. F.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 480-481.

In 25 experiments on unanesthetized dogs the threshold dose of adrenin was 0.0001 mg. per kilo of animal, and the dose producing the maximum blood concentration was 0.01 mg. per kilo. It took about 10 minutes for the blood to return to normal. In the example given the specific gravity of the blood showed a change from 1.0504 to 1.0562, a maximum, two minutes after injection. Anhydremia resulting from excitement resembles the above but is not dependent on the splanchnic control of the liver, spleen or adrenals, for in five dogs this reaction occurred to the same extent after splanchnotomy as it did when these nerves were intact.

—J. C. D.

Adrenalectomy and its relation to the metabolism of the cat. Barlow (O. W.), Am. J. Physiol. (Balt.), 1924, **70**, 453-464.

After removal of one adrenal, the total metabolism is initially depressed but gradually returns to or above the preoperative level. When the basal metabolic rate is computed on the body weight basis, two types of results are noted. In 25% of the series studied a new basal level 14% below their respective normals was established at the fifth month and maintained until the end of the experiment. The body weight of this group increased markedly due to a deposit of fat. In 75% of the series the metabolic rate and body weight had returned to or above normal at the fifth month. After removal of both glands, the animals survived on an average for 40 hours, the extremes being 104 and 7½ hours, respectively. The basal metabolic rate fell at first, rose to near normal at the sixth hour and then progressively fell. The body temperature fell, then rose above normal by the tenth hour, and fell gradually to normal at the thirtieth hour. Thereafter a rapid drop was noted until death. The fall in metabolism as well as body temperature appeared accelerated 4-6 hours before death, at which time the blood pressure and blood sugar also showed a rapid decline.—Author's Abst.

Conditions of activity in endocrine glands, XVI. The rôle of the adrenal medulla in pseudaffective hyperglycemia. Bulato (S.

W.) & Cannon (W. B.), Am. J. Physiol. (Balt.), 1925, **72**, 295-313.

The pseudaffective state described by Cannon and Britton is attended by a hyperglycemia which increases as time passes. If decerebration is not followed by pseudaffective activity the glycemic percentage does not increase markedly and may fall. If the adrenal glands have been removed, or if one has been removed and the splanchnic supply of the other has been destroyed, the initial hyperglycemia of the pseudaffective state neither rises nor remains high; instead it declines. If the hepatic nerves have been severed without disturbance of the adrenal glands the initial hyperglycemia is increased during quasi-emotional activity. Insulin is effective in reducing the hyperglycemia that follows decortication, even though pseudaffective phenomena are prominent and the pituitary body is intact. The relation of the adrenal medulla to hyperglycemia is discussed, and the weak evidence and the erroneous logic leading to the conclusion that it plays no important rôle, are pointed out. Also the claim that there is pituitary involvement in decerebrate hyperglycemia is questioned and reasons are advanced for discrediting that claim.

—Author's Abst.

The effect of roentgen rays on the suprarenal gland. Martin (C. L.), Rogers (F. T.) & Fisher (N. F.), Am. J. Roentgenol. (N. Y.), 1924, **12**, 466; abst., Am. J. Dis. Child., **30**, 437.

The conclusions of these authors do not coincide with the clinical conclusions of recent observers. Their conclusions in this preliminary report are that direct heavy radiation of the isolated left adrenal administered following the removal of the right adrenal of a dog produced no symptoms during practically a month of observation, although a marked fibrosis occurred in the radiated gland. The same dose produced cachexia and death when applied to an isolated loop of small intestine and marked fibrosis when applied to the upper pole of the kidney.

On the adrenalin hyperglycemia. Ohara (T.), Tohoku J. Exper. Med. (Sendai), 1925, **6**, 213-247.

A study was made in rabbits of the effects of pancreas extract made by Kumagai's method. It was found that the extract suppressed adrenalin hyperglycemia when the dose of the latter was not too great. It also caused lowering of the blood sugar in normal animals and in other experimental hyperglycemia. It was found to have a more powerful effect by subcutaneous injection than by intravenous application. The pancreatic extract had no influence upon the normal blood pressure and did not lower the pressure raised previously with adrenalin. Perfusion of the extract through the peripheral blood vessels by the Laewen-Trendelenburg's method

caused no change in the rate of the outflow of Ringer's solution. The extract produced no change in the enucleated frog's-eye-pupil either in the normal state or in adrenalin mydriasis. It had no effect on the pupils of dogs either normal or depancreatized. The rise of blood sugar caused by piqûre was markedly reduced by the subcutaneous injection of the extract. Pituitrin had no obvious inhibiting influence upon the fall of blood sugar caused by the pancreatic extract. The pancreatic extract had no effect upon the contraction of the surviving uterus strip of the cat either in normal condition or when contracted with adrenalin.—R. G. H.

Effect of adrenalin on the venous blood from the bone marrow (Untersuchungen am Knochenmarksvenenblut des Hundes. I. Die Wirkung des Adrenalins auf das Blutbild). Schoen (R.) & Berchtold (E.), Arch. f. exper. Path. u. Pharmakol. (Leipz.), 1925, 105, 63-75.

Experiments were made on large dogs under urethane narcosis. It was found that the blood of the nutrient tibial vein shows constant differences from normal blood; there is an excess of neutrophiles, and there are more young forms of red and white cells. Adrenalin causes these young forms to be washed out of the marrow, the effect reaching its height in about 10 minutes after the injection. Adrenalin causes no change in peripheral blood beyond a leucocytosis. Whether the increased cell output is due to stimulation of the marrow or to circulatory changes was not determined.—R. G. H.

Chromaffin cell tumor of the suprarenal medulla (paraganglioma). Zeckwer (I. T.), Boston M. & S. J., 1925, 193, 254-258.

A tumor of comparatively rare type is described arising from the suprarenal medulla, which was an incidental finding at autopsy in the case of a woman of 56 years of age who died suddenly from cerebral thrombosis. The tumor appeared as an ovoid mass 4x3.5x2.5 cm., occupying the medulla of the left suprarenal gland and surrounded by a greatly narrowed zone of cortical tissue. Microscopically it was composed of chromaffin cells arranged in cords separated by dilated anastomosing capillary channels. Many of the cells, illustrated by photomicrographs, assumed bizarre giant forms with multiple nuclei and vacuolated cytoplasm. Though distinctly benign, the proliferating cells had in places extended through the entire cortical zone, but had not penetrated the capsule. The opposite suprarenal was of usual gross appearance and presented no microscopic change.—Author's Abst.

The digestive tract and endocrine function. Lockwood (B. C.), J. Am. M. Ass. (Chicago), 1925, 85, 1932-1036; abst., A. M. A.

Lockwood reports the results of a clinical investigation based

on a study of the gastro-intestinal tract of most of the frank endocrine cases, involving the thyroid, pituitary and suprarenal glands, which have come under his observation during the past few years. He summarizes as follows: The gastro-intestinal tract shares with the rest of the organs of the body in the secondary effects resulting from disturbances in the functions of the endocrine glands, but not to the extent that is often considered. The exact mechanism is not definitely known, but it is probably through both the medium of the autonomic nervous system and changes in the general bodily nutrition. Slight endocrine disorders seldom produce gastro-intestinal disturbances. In general, the stomach acidity tends to be lowered by hyposecretion of the thyroid, pituitary and suprarenals. Hyperthyroidism also tends to reduce gastric acidity, achlorhydria being a frequent finding in exophthalmic goiter cases presenting gastrointestinal symptoms. Peptic ulcer is not common in manifest endocrine disease, having been noted only four times in 126 cases. In endocrine cases in which there is intestinal disorder, the most common lesion is spastic rather than atonic. In gastro-intestinal cases, all other etiologic factors should be excluded before incriminating the endocrine glands.

Changes in the endocrine organs and brain in schizophrenia (dementia precox) [Über Veränderungen endokriner Organe und des Gehirns bei Schizophrenie (Dementia praecox)]. Münzen (F. T.) & Pollok (W.), Ztschr. f. d. ges. Neurol. u. Psychiat. (Berl. u Leipz.). 1925. 95, 376-410; abst., Arch. Neurol. & Psychiat., 14, 531.

The authors describe a case of dementia precox of short duration with histologic examination of all the organs after death. The clinical signs ran a course of only six months before death occurred, and histologic examination was particularly favorable because necropsy was performed hardly three hours after death. Necropsy showed nothing in the organs outside the central nervous system No evidence of tuberculosis was present, so that the changes which might have occurred from this disease can be ruled out The hypophysis showed in its anterior lobe an extraordinary increase in the basophilic cells. They were so numerous as to make the use of higher magnifications unnecessary, and to crowd out all other cells. Eosinophils were present in normal numbers. In the anterior portion of the orohypophysis was an adenoma about 1.5 mm. in diameter. Not infrequently in the anterior lobe of the hypophysis were seen groups of cells arranged around small lumens filled with colloidal material. The pars intermedia was separated by a space lined with epithelium which connected directly with the epithelium of the base of the anterior lobe. In the posterior lobe large masses of eosinophilic cells were seen, often arranged in groups. The thyroid gland showed a colloidal structure

throughout. In all parts of the gland were small adenomatous formations of cells. The epithelium of the gland was higher than normal. Other than this no changes were visible in the thyroid, which the authors considered about normal in structure. The parathyroids showed a decided decrease in the parenchyma due to large deposits of fat. The picture was similar to that found in the parathyroids of old people or in wasting illness such as carcinoma. The suprarenals showed a great deal of lipoid material in the cortex, particularly in the zona fasciculata. The medulla was very thin in relation to the cortex. The chromaffin cells were arranged in heterogeneous ways. In the pancreas was a diminution in the number of the islands of Langerhans, but the histologic structure of these bodies was normal. The ovaries showed a cystic degeneration. The liver, uterus and thymus were normal. Some of the more important literature is abstracted.—R. G. H.

Progressive lipodystrophy. Watson (W. N. B.), & Ritchie (W. T.), Quart. J. Med. (Oxford), 1925, 18, 224-239.

The authors report two new cases and review the literature dealing with this condition. They conclude from this study that lipodystrophy is probably of nervous. and not of endocrine, origin.
—J. P. S.

Gerodermia and eunuchoidism. Izzo (R. A.), Rev. méd. Lat.-Am. (Buenos Aires), 1925, 10, 988-1005; abst., J. Am. M. Ass., 85, 1339.

Izzo describes with illustration a case of eunuchoidism with dystrophy of the skin and genitals in a woman, aged 38, who seemed to be over 60, and presented symptoms suggesting thyroid insufficiency and perverted pituitary functions, with curvature of the spine and genu valgum. In another case the man, aged 66, presented gerodermia of the genital dystrophia type with the same clinical picture as the woman. The two cases confirm the gerodermia variety of eunuchoidism, and its practical identity in men and women, although in the latter it should be called ovarodystrophic gerodermia.

Demonstration of estrus-inducing substances in the blood of females. Loewe (S.), Klin. Wchnschr. (Berl.), 1925, 4, 1407; abst., Chem. Abst., 19, 2976.

Blood was collected in the pro-estrus period. The blood of rabbits, cows and women was found to contain estrus-inducing substances, presumably the specific ovarian hormone.

The physiological action of ovarian fluid (Zur Frage der physiologischen Wirkung der Ovarialflüssigkeit). Yeresin (W. J.),

Petrowsky (W. W.), & Maloff (G. A.), Arch. f. d. ges. Physiol. (Berl.), 1925, **209**, 170-176.

Ovarian fluid of cattle produces a marked stimulating action of long duration on the frog's heart, shown by increase of amplitude both of systole and diastole. Usually a similar effect is produced on the rabbit's heart. There is no effect on the frog's liver-vessels, but a constricting effect on those of the rabbit's ear.—A. T. C.

Quantitative studies on the pars tuberalis of the hypophysis cerebri. Atwell (W. J.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 499-500.

The pars tuberalis was compared in volume to the pars intermedia. In the tailed amphibia the pars tuberalis was larger, in one case 5 times larger than the pars intermedia. In the anura it was only 1-23 as large as the pars intermedia. In cats it runs from $\frac{1}{4}$ to over $\frac{3}{4}$ the size of the pars intermedia. A table of *the results in the cat is given.* The author concludes that in a number of vertebrate forms the volume of the pars tuberalis is equal or nearly equal to that of the pars intermedia, and that as far as volume is concerned the pars tuberalis may be capable of producing an important secretion in forms as high as the mammals.—J. C. D.

The effect of pituitrin on the fatty acid of the liver. Coope (R.) & Chamberlain (E. N.), J. Physiol. (Lond.), 1925, **60**, 69-77.

Injection of extract of posterior lobe of the pituitary body into rabbits (3 to 4 cc.) and rats (1 to 2 cc.) is followed by a well marked increase in the amount of fatty acid in the liver. The *time relations of this effect are more consistent if the extract is* given with gum arabic solution. The fatty acid infiltration after pituitrin with gum reached its maximum between 10 and 15 hours, and disappeared before the 30th hour. The infiltration does not occur if the pituitrin has been previously submitted to such treatment as destroys its oxytocic and pressor constituents. Control experiments with extracts of other tissues have, up to the present, failed to produce fatty infiltration of the liver.—R. G. H.

Studies on experimental hypophysectomy. 1. Effect on the maintenance of life. Dandy (W. E.) & Reichert (F. L.), Johns Hopkins Hosp. Bull. (Balt.), 1925, **37**, 1.

The authors bring forth the question again of the assumption that the hypophysis is essential to life because past data concerning hypophysectomy have given rise to two views: some maintain its necessity, and some think death is caused in the animals by brain injury. Two different operative techniques have been used in the past, the buccal approach (all these animals have died) and the

temporal approach (some of these animals have lived). The authors chose the latter because of less brain injury. Three things stand out in their technique, namely, inverting the head 100° to 135° so the brain will fall away from the base of the skull, releasing as much cerebro-spinal fluid as possible, and using hypertonic-salt solution intravenously which causes brain substance to shrink. They believe the set of symptoms described as due to pituitary removal to be in reality due to brain injury and post-operative increase of intracranial pressure. They conclude, as the dogs lived from a few days up to one year after hypophysectomy, and many of these animals were subjected to a careful necropsy for remaining pituitary tissue, that the hypophysis is not essential in life. Tables are included. The operative procedure is given in detail.—H. P. Rush.

Pituitary disorder. Frazier (C. H.) & Grant (F. C.), J. Am. M. Ass. (Chicago), 1925, 85, 1103-1106; abst., A. M. A.

Out of 175 cases of pituitary disorder, Frazier and Grant have selected 100 cases for analysis of symptoms and results of treatment. In this series of 100 cases, the initial symptom, according to the patient's statement, was failing vision in 71%, and a later development in 16%. In 27%, headache was the initial symptom, and a later symptom in 61%; it was described as severe in 37%, as moderate in 15%, and as slight in 9%. "Pituitary headache" implies tension within the pituitary capsule, and one would rather expect a more or less constant location to which the pain is referred. As a matter of fact, in this series the location was varied and was described as frontal (17), fronto-occipital (5), fronto-temporal (7), vertexfrontal (1), occipital (5), vertexoccipital (2), occipitotemporal (3), temporal (3) and general (7). Thus the majority in this series were frontal, followed in order of frequency by occipital, general and bitemporal. While headache was recorded as severe in one-third of the total number of cases, as a matter of fact in only 5 cases was it the outstanding symptom for which the patient sought relief. Optic atrophy was present in 41%, and in more than half of these there was total or almost complete blindness in one eye, with deterioration of vision in the other. The yellowish discoloration of the disk, really pathognomonic of pituitary disease, was recorded in 35% of the cases. The authors state that the surgery of the pituitary body, as practiced today, has limitations, proportionate in large measure to the duration of the lesion. When surgery is recognized as an essential factor in the treatment of the pituitary lesion in the early stage, before optic atrophy is advanced and before the terminal stages of functional disorder are reached, there will be a decided improvement in the operative results and a lower mortality. The surgeon has been handicapped because he has been confronted so often with terminal effects.

Pituitary obesity and adolescence. Gardiner-Hill (H.), Jones (I.), & Forrest-Smith (J.), Quart. J. Med. (Oxford), 1925, **18**, 309-326.

This paper is based upon a study of 60 patients (22 males and 38 females, of ages from 8 to 20 years) in whom the onset of obesity developed concurrently with adolescence, i. e., with a period of accelerated growth. There were no neighborhood symptoms indicating a primary lesion in the pituitary, hence the authors consider the condition the result of disturbed pituitary function. Apart from the obesity the chief characteristic of these patients is an early tendency to overgrowth and premature development, which appears to be due to hyperpituitarism (anterior lobe hyperactivity). This condition finally passes into hypopituitarism. In the early stages there is an inability to use carbohydrate; in the later stages, an increased sugar tolerance. This increased tolerance is not due so much to increased oxidation of carbohydrate, but to an increased power of storage. It is suggested that this may in some way be connected with a hyperactivity of insulin, which is no longer controlled in the normal manner by the pituitary hormone.—J. P. S.

Hypophysis and Raynaud's disease (Hypophyse und Raynaudsche Krankheit). Kopf (H.), München. med. Wchnschr., 1925, **72**, 940.

In three patients with Raynaud's disease Kopf found that injections of hypophysin (2 cc.) resulted in almost immediate relief of the cyanosis. After a few days' treatment with hypophysin, hypophysis tablets were substituted with lasting benefit.
—R. G. H.

The accuracy of standardization of pituitary preparations with the isolated uterus (Ueber die Genauigkeit der Eichung von Hypophysenpräparaten am isolierten Uterus). Sawasaki (H.), Arch. f. d. ges. Physiol. (Berl.), 1925, **209**, 137-169.

Using Dale and Laidlaw's method with the virgin guinea-pig uterus, as modified by later workers, the probable error is about 4.5%. In 88% of cases the error found was within 10% and in 120 experiments the extreme divergence was 16%. Usually 2 to 3 animals are necessary for a standardization. With Kochmann's method the probable error is about 8%, and the greatest error found in 38 experiments was 22.3%.—A. T. C.

Researches on insulin. I. Is insulin an unstable sulphur compound? Abel (J. J.) & Geiling (E. M. K.), J. Pharmacol. & Exper. Therap. (Balt.), 1925, **25**, 423-448.

Crystalline amino acids; protein-like fractions of varying sulphur content and low phosphorus content, and protein-like fractions having a medium or relatively low sulphur content and a

high phosphorus content were separated from Iletin (Lilly) (8 and 12 rabbit units per milligram). It was possible completely to remove the active insulin from each of these fractions so that they no longer showed a trace of the hormone. In the course of the purification the insulin rabbit unitage was raised from 8 to 12 to more than 40. It was shown that when an "insulin" of high unitage is boiled for a short time with N/10 Na₂CO₃ the resultant physiological inactivation is always associated with an alteration in the linkage of a part, if not all, of the sulphur of the hormone. Ammonia is not liberated by this treatment. Inert fractions contain very little of this labile sulphur, and in all fractions the content of labile sulphur, more especially what is called the "sodium carbonate sulphur," appears to be directly proportional to the degree of hypoglycemic activity. Phosphorus was not found to be a constituent of insulin.—G. E. B.

Inactivation and reactivation of insulin. Allen (R. S.) & Murlin (J. R.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 492-493.

Insulin in weak hydrochloric acid can be inactivated by the hydrogen liberated when the acid attacks tinfoil on the cork of the container. Commercial hydrogen produces the same result. Oxygen reactivates it. A chart showing results of such procedures on the physiological action of insulin is given. It shows that reduced insulin may raise the blood sugar level.—J. C. D.

Note on the relationship between insulin and trypsin. Brand (E.), & Sandberg (Marta), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 428-431.

The authors conclude that insulin combines with trypsin not as an inhibitor of trypsin. Trypsin combining with insulin inhibits the action of the latter, at first reversibly and later irreversibly, probably by digestion. It is possible that further study of the nature of the insulin-enzyme reaction will help to decide whether proteolytic enzymes can act without the formation of an intermediate compound between enzyme and substrate.—J. C. D.

Blood urea and its estimation in diabetes mellitus. Brunton (C. E.), Quart. J. Med. (Oxford), 1925, **18**, 241-249.

Brunton studied the blood urea of 14 diabetic patients, using Twort and Archer's method. No relation was found between the amounts of blood sugar and blood urea. The administration of insulin did not alter the concentration of blood urea. The duration of diabetes mellitus does not necessarily increase the concentration of blood urea. Diabetic coma was not found to be necessarily accompanied by an abnormal blood urea concentration.—J. P. S.

Effect of insulin on the metabolism of dogs under amytal anesthesia. Deuel (H. J.), Chambers (W. H.) & Evengen (J.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 424-425.

Amytal produces prolonged anesthesia when injected into dogs. It does not influence the blood sugar. Usually there is increased heat production following insulin, suggesting an increased fat metabolism. Sometimes there is an increase in the respiratory quotient. The blood sugar responds as it would in unanesthetized animals.—J. C. D.

The reactivation of inactivated insulin in vitro and in vivo. Epstein (A. A.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 422-423.

Insulin inactivated by trypsin can be reactivated in vitro by pepsin, safranin and cryogenin (M-Benzaminosemicarbazide). The blood of rabbits injected with one of these substances and then immediately injected with inactivated insulin shows the characteristic effect of active insulin. These substances are, therefore, effective in the body as well as in the test tube.—J. C. D.

The relation of infection to diabetic coma. Graham (G.), Quart. J. Med. (Oxford), 1925, **18**, 294-299.

On the basis of a study of 7 cases, Graham concludes that a general or local infection is often the direct cause of the onset of coma in a patient who has diabetes mellitus. In the presence of such an infection insulin is much less effective in lowering the blood sugar.—J. P. S.

Glycogenolytic action of insulin. Müller (E. F.) & Petersen (W. F.), J. Am. M. Ass. (Chicago), 1925, **85**, 820-823.

The authors present the importance of knowing how insulin acts when introduced into the mammalian body and what organs participate in the increased sugar metabolism. On administering like dosages of insulin subcutaneously, intravenously and intradermally it was found that after 2 hours the intradermally injected insulin exceeds the others in duration and intensity of effect. The authors theorize to the effect that the intradermal injections give "parasympathetic" stimulation, apparently regarding the cutaneous afferent fibers as belonging to the parasympathetic group.
—R. G. H.

Studies on the ultrafiltration and electrodialysis of insulin solutions. Taylor (T. C.), Brawn (C. E.) & Scott (E. L.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 453-454.

Insulin (Lilly) when subjected to electrophoresis and dialysis combined is separated into two fractions, one of which has 100%

greater physiological activity than the original product. A crystalline precipitate can be obtained from this.—J. C. D.

Experiments with extracts of parathyroid glands. Fisher (N. F.) & Larson (E.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 447-448.

The authors used ox gland extract and injected dogs with it. Their results agree with those reported by Collip.—J. C. D.

The hormone of the parathyroid gland. Hanson (A. M.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 560-561.

This gives the author's method of preparing a stable extract of the gland containing the active principle as described also by Collip.—J. C. D.

Pineal precocity (Die epiphysäre Frühreife). Odermatt (W.), Schweiz. med. Wchnschr. (Basel), 1925, **55**, 474-478; abst., Am. J. Dis. Child., **30**, 426.

The author gives the clinical picture of a boy, aged 4½ years, with an essentially negative family and past history, who at 6 months revealed considerable adiposity, the first appearance of pubic hair and a generally precocious physical development. When at 18 months he began to talk his voice was deep. At time of writing he had the appearance of a boy aged 14. A beard is commencing to make its appearance. The axillary and pubic hair growth is thick. Both testicles are slightly but symmetrically enlarged. The breasts reveal no glandular development. The mental status is that of a 6 or 7-year-old child. A Binet-Simon test by Professor Bing shows a mental age of 6 years 4 months and an intelligence quotient of 148. The heart, lungs, abdomen, urine, blood and Wassermann examinations were negative; the roentgen ray reveals no enlargement in the neighborhood of the adrenals. The author believes the case to be due to a disorder of the pineal gland. He has instituted organotherapy.

On the relation of thyroid secretion to specific dynamic action. Bauman (E. J.) & Hunt (Louise), J. Biol. Chem. (Balt.), 1925, **64**, 709-720.

The specific dynamic action of glucose was determined several times in 10 normal rabbits and at various intervals after thyroidectomy in 9 rabbits. In normal rabbits the extra heat produced in 4 hours at intervals from ½ to 4½ hours after feeding 25 gm. glucose averaged about 5 calories. Complete thyroidectomy caused a gradual decrease and final disappearance of specific dynamic action after about 65 days. Restoration of specific dynamic action which had entirely disappeared following thyroid removal

was accomplished by feeding thyroid gland.   Incomplete thy-
roidectomy caused a decrease of specific dynamic action which was
increased in some cases by feeding a small amount of potassium
iodide.—Authors' Abst.

The geographic distribution of exophthalmic goiter in the British
    Isles. Campbell (J. M. H.), Quart. J. Med. (Oxford), 1925, 18,
    191-223.

    This paper was based upon a study of statistics in the Registrar-
General's office for from 7 to 10 years. In general, it was found that
exophthalmic goiter was most common in Cornwall, Devon and
Somerset and least frequent in the densely populated districts,
Essex, Middlesex and Hertford. Morbidity and mortality statistics
were higher for the country districts than for the towns. Where
exophthalmic goiter was unduly prevalent the birth rate was often
lower, both of which conditions may have been due in part to social
and industrial factors.—J. P. S.

Pathology of exophthalmic goiter—a histological and chemical study
    of the changes following the administration of iodin (Lugol's solu-
    tion). Cattell (R. B.), Boston M. & S. J., 1925, 192, 989-996.

    The report is based on careful studies of 168 surgical specimens
removed from 125 subjects. From a study of the histology and
iodin content of the thyroid glands it was found that in 87.9% of
patients with exophthalmic goiter receiving iodin therapy, there was
an involutional change in the thyroid gland; 6.7% showed an in-
creasing hyperplasia. There was an increase in the iodin content of
all glands after iodin administration. The iodin content was direct-
ly proportional to the involutional change, up to a certain point.
Similar changes followed superior pole ligations and hemi-thyroid-
ectomy together with rest, but it was most marked after iodin alone.
The clinical improvement after iodin administration bore a relation
to this structural and especially chemical change. A group of
patients showed marked involutional change and a high iodin con-
tent in their glands, yet still suffered from severe exophthalmic
goiter. The pathology of exophthalmic goiter was not constant;
parenchymatous hyperplasia was seen superimposed on adenomata
and endemic goiters. Lymphoid infiltration occurred usually and
remained to some degree after involution.—J. C. D.

Inevitable damage consequent upon goiter. Coller (F. W.), Boston
    M. & S. J., 1925, 193, 545-550.

    A discussion without quotation of experimental or clinical data.
The author concludes that endemic goiter is composed of colloid
and adenomatous elements. In early life the colloid element pre-
dominates; after 25 the adenomata predominate. These changes

are progressive and constant and in time, the length of which is well established, will cause the appearance of symptoms. Frank hyperthyroidism caused by endemic goiter increases in frequency from the latter part of the third decade to the fifth and sixth decades when at least a third of the subjects have it. Definite cardiovascular damage appears in at least a fourth of those with hyperthyroidism and in a smaller but appreciable number of those with normal metabolic rates. Endemic goiter is a precancerous lesion with an incidence of malignancy of at least 3%. Endemic goiter causes many mental changes of a minor but disabling nature and in those with a psychopathic inheritance may excite the appearance of some mental abnormalities. The progressive nature of the goiter and the appearance of symptoms permits an attack of the goiter at a time when medication has ceased to be effective and when the changes begin to menace the health of the patient. The surgical removal of the adenomatous goiter at this time prevents the appearance of the great morbidity otherwise to be expected. The removal of adenomatous goiters should be advised on diagnosis in patients if over twenty-five years.—J. C. D.

Some factors of significance in adolescent goiter. Gardiner-Hill (H.), Brett (P. C.), & Forrest-Smith (J.), Quart. J. Med. (Oxford), 1925, 18, 133-142.

Of 100 cases of adolescent goiter 79% were of the colloid type, 16% exophthalmic, 3% adenomatous, and 2% endemic. In colloid goiter the function of the thyroid was apparently normal in 42% of the cases; in 32% there was evidence of hyperthyroidism, and in 26% evidence of hypothyroidism. A large majority of these patients were above the normal height for the age; those with hyperthyroidism were below weight and those with hypothyroidism were above weight normal for the age. Menstruation was normal in about one-half of the patients with colloid goiter; but delayed, irregular and scanty in hyperthyroidism; and excessive in hypothyroidism. Menstruation was normal in one-fourth of the cases of exophthalmic goiter; in the remainder it was frequently absent. Estimations of basal metabolism corresponded to the results obtained in adults for similar conditions, but the variations from normal were not so great. In both hyper- and hypo-thyroidism there was a definite delay in the blood sugar curve, though hyperthyroidism produced a higher blood-sugar content.—J. P. S.

Carbohydrate tolerance in myxoedema. Gardiner-Hill (H.), Brett (P. C.), & Forrest-Smith (J.), Quart. J. Med. (Oxford), 1925, 18, 327-331.

This paper records the findings in 15 well marked cases of myxedema. The authors conclude that severe cases of exophthalmic goiter tend to be accompanied by high and prolonged blood-sugar

the chromophobe vacuoles and the colloid is a mixture of the two. The secretion reaches the blood by passing back between the cells. The interstitial cells have the same function as do the cells of the follicles. Their secretion is not stored as colloid. The chromophobe secretion was increased in all hyperactive glands studied, and it is believed that it contains the active principle of the gland. The chromophile secretion varied independently of the activity of the gland, and it is believed that it does not contain the active principle of the gland, but acts as a medium for concentrating the active principle and storing it as colloid.

The mitochondria were increased in all hyperactive glands studied, but were also increased in certain areas of non-toxic adenomas. The increase in mitochondria bore no constant relation to the activity of the glands as indicated by the basal metabolism. It is believed that the mitochondria do not produce the secretion antecedents directly, but that they have some function in the general metabolism of protoplasm and are not responsible for the specific activities of the cells which contain them. No abnormal secretory antecedents were demonstrable in either toxic adenomas or exophthalmic goiters. In all of the glands studied an attempt was made to estimate the amount of stroma, amount of parenchyma, amount of colloid, density of colloid, vacuoles in the colloid, size of cells, mitochondria in cells, chromophobe secretion in cells and chromophile secretion in the cells.

—Author's Abst.

Use of iodine in goiter. Lahey (F. H.), Boston M. & S. J., 1925, 193, 487-490.

This paper is based on the same studies as Cattell's (abst. in this issue). Proper administration of Lugol's solution increased the percentage of cases in which thyroidectomy can be performed in a single stage. The amount of thyroid left in place at operation should be greater than in patients not treated with iodine, for involution of the gland takes place and the thyroid tissue in iodine-treated patients is not so active as in the untreated.—J. C. D.

Insulin in treatment of hyperthyroidism. Puchulu (F.), Rev. Soc. med int. (Buenos Aires), 1925, 6, 140-164; abst., J. Am. M. Ass., 85, 1098.

Puchulu states that treatment with 5 or 10 units of insulin had a favorable influence on the general condition; the weight increased and the patients became more tranquil, but the vegetative functions, the pulse, the systolic blood pressure, the glycemia, basal metabolism and menstruation did not seem to be influenced by the insulin. In the discussion, Waldorp mentioned a case of exophthalmic goiter with material improvement under insulin treatment.

Insulin treatment of exophthalmic goiter. Senga (H.), J. Orient. Med. (Dairen, S. Manchuria), 1925, 3, 62; abst., J. Am. M. Ass., **85**, 1007.

Three cases of exophthalmic goiter were treated with insulin by Senga with good results. Remarkable improvement was observed; the basal metabolic rate diminished; the body weight increased and the general nervousness and tremor of the patients subsided. Although the lessening of struma and exophthalmos was but slight, the general feeling of the patient appeared to be much better in every way.

Nutritional changes in exophthalmic goiter. Sturgis (C. C.), & Greene (J. A.), Arch. Int. Med. (Chicago), 1925, **36**, 561-578.

The relation between the food intake, basal metabolism and body weight in patients with exophthalmic goiter has been emphasized. From our present observations, which are in accord with those made previously, it is concluded that in order to maintain body weight while resting in bed the food intake in a patient with exophthalmic goiter and an elevated metabolism must be at least from 75% to 100% greater than the basal metabolism. A study of the histories of 65 patients with exophthalmic goiter indicated that although 88.5% of them had an appetite which was classified as ravenous, increased or normal, yet 86.5% of these patients gave a history of a loss of 11.9 kg. (26.3 pounds) of body weight in 11.9 months. A comparison of the body weight of these 65 patients with the standard weight tables shows that 80.2% averaged 18.2% below normal when they first appeared at the hospital. A study of the alteration in body weight following operation in 36 patients who had not been treated with Lugol's solution and therefore were operated on with an elevated metabolism, averaging plus 39, showed that all except one, in whom the weight was unchanged, lost an average of 5.2% of their preoperative body weight in an average of 11 days after the operation. The factors responsible for this loss of weight might be several, but it was concluded that the most important was the combination of the inability of the patient to consume normal quantities of food and the elevated metabolism, which may remain high for a period of 10 days or longer following thyroidectomy. A second group of 28 patients, who had been treated with Lugol's solution and in whom the metabolism was reduced to an average of plus 21 before the operation, was studied. In these patients, 18% had actually gained weight by the tenth postoperative day, and the loss of weight for the entire group averaged only 2%. This loss is even less than the average decrease in body weight following operation in a group of 25 patients with colloid goiters and nontoxic adenomas.—Authors' summary.

Physical-chemical changes of the blood in thyroidectomized guinea pigs. Wilhelmj (C. M.) & Fleisher (M. S.), Proc. Soc. Exper. Biol. & Med. (N. Y.), 1925, **22**, 478-480.

In thyroidectomized animals there is an increased surface tension of the blood plasma. There is marked individual variation but on the average it is noticeable on the eighteenth day and reaches a maximum between the twenty-second to the twenty-eighth day. The maximum increase varies from 5.1 to 5.7 dynes. There seems to be an increase in the viscosity of the plasma.

—J. C. D.

Annual Index

Authors

Subjects